FOR TELEHEALTH REGISTRANTS SECOND OR SUBSEQUENT OFFENSE:	Not applicable to teleheath registrants.	
(76) Promoting or advertising through any communication media the use, sale, or dispensing of any controlled substance appearing on any schedule in Chapter 893, F.S. (Section 459.015(1)(tt), F.S.)		
FIRST OFFENSE:	Letter of concern and a $1,000.00 fine.	1 year suspension, followed by a period of probation, and a $5,000.00 fine.
SECOND OFFENSE:	Reprimand and a $5,000.00 fine.	1 year suspension, followed by a period of probation, and a $10,000.00 fine.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	1 year suspension with a corrective action plan.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Reprimand.	1 year suspension with a corrective action plan.
(77) Failure to comply with the controlled substance prescribing requirements of Section 456.44, F.S. (Section 456.072(1)(mm), F.S.)		
FIRST OFFENSE:	Suspension of license for a period of six (6) months followed by a period of probation and an administrative fine in the amount of $10,000.00.	Revocation and an administrative fine in the amount of $10,000.00 or denial of licensure.
SECOND OFFENSE:	Suspension of license for a period of one (1) year followed by a period of probation and an administrative fine in the amount of $10,000.00.	Revocation and an administrative fine in the amount of $10,000.00 or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Suspension of license for a period of six (6) months with a corrective action plan.	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension of license for a period of one (1) year with a corrective action plan.	Revocation or denial of licensure.
(78) Providing false or deceptive expert witness testimony related to the practice of medicine. (Section 459.015(1)(qq), F.S.)		
FIRST OFFENSE:	Reprimand and an administrative fine of $5,000.00; if false representation, a reprimand and a $10,000.00 fine.	Revocation and an administrative fine of $10,000.00 or denial of licensure.
SECOND OFFENSE:	Suspension and an administrative fine of $7,500.00; if false representation, suspension and a $10,000.00 fine.	Revocation and an administrative fine of $10,000.00 or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand.	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension.	Revocation or denial of licensure.

(79) Failure to comply with the requirements of Section 390.0111(3), F.S., regarding termination of pregnancies. (Section 456.072(1)(k), F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	A period of probation and an administrative fine in the amount of $2,500.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $2,500.00.	Suspension followed by a period of probation and an administrative fine in the amount of $5,000.00.
THIRD OFFENSE:	Reprimand and an administrative fine of $5,000.00.	Revocation and an administrative fine in the amount of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Suspension with a corrective action plan.
FOR TELEHEALTH REGISTRANTS SECOND OR SUBSEQUENT OFFENSE:	Reprimand.	Revocation.
(80) Dispensing a controlled substance listed in Schedule II or Schedule III in violation of Section 465.0276, F.S. (Section 459.015)(1)(uu), F.S.)		
FIRST OFFENSE:	Probation and an administrative fine of $5,000.00.	Revocation and an administrative fine of $10,000.00 or denial of licensure.
SECOND OFFENSE:	Suspension followed by a period of probation and an administrative fine of $5,000.00.	Revocation and an administrative fine of $10,000.00 or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	One (1) month suspension with a corrective action plan.	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Six (6) month suspension with a corrective action plan.	Revocation or denial of licensure.
(81) Willfully failing to comply with Section 627.64194 or 641.513, F.S. with such frequency as to indicate a general business practice. (Sections 459.015(1)(vv), and 456.072(1)(oo), F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	Reprimand and an administrative fine of $5,000.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $5,000.00.	Revocation and an administrative fine of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Reprimand.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Reprimand.	Revocation.
(82) Issuing a physician certification as defined in Section 381.986, F.S., in a manner out of compliance with the		

requirements of that section and the rules adopted thereunder. (Section 459.015(1)(ww), F.S.		
FIRST OFFENSE:	Denial or probation and an administrative fine of $1,000.00.	Denial or revocation and an administrative fine of $5,000.00.
SECOND OFFENSE:	Denial or suspension and an administrative fine of $5,000.00.	Denial or revocation and an administrative fine of $10,000.00.
FOR TELEHEALTH REGISTRANTS	Not applicable to telehealth registrants.	
(83) Failure to consult the prescription drug monitoring system, as required by Section 893.055(8), F.S. (Section 459.015(1)(g), F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	Reprimand and an administrative fine of $2,500.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $2,500.00.	Suspension and an administrative fine of $5,000.00.
THIRD OFFENSE:	Suspension and an administrative fine of $5,000.00.	Revocation and an administrative fine in the amount of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Reprimand.
FOR TELEHEALTH REGISTRANTS SECOND OR SUBSEQUENT OFFENSE:	Reprimand.	Revocation.
(84) Failure to report adverse incidents in planned out-of-hospital births by Section 459.015(1)(g), F.S. (Section 459.015(1)(g), F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	Reprimand and an administrative fine of $2,500.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $2,500.00.	Suspension and an administrative fine of $5,000.00.
THIRD OFFENSE:	Suspension and an administrative fine of $5,000.00.	Revocation and an administrative fine in the amount of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Reprimand.
FOR TELEHEALTH REGISTRANTS SECOND OR SUBSEQUENT OFFENSE:	Reprimand.	Revocation.
(85) Performing a liposuction procedure in which more than 1,000 cubic centimeters of supernatant fat is removed, a Level II office surgery, or a Level III office surgery in an office that is not registered with the department pursuant to Section 458.328 or 459.0138, F.S. (Section 459.015(1)(xx), F.S.)		
FIRST OFFENSE:	Twelve (12) months probation and an administrative fine of $5,000.00 per day.	Revocation and an administrative fine of $5,000.00 per day, or denial of licensure.

SECOND OFFENSE:	Twelve (12) months suspension followed by a term of probation and permanent restriction from performing office surgery and an administrative fine of $5,000.00 per day.	Revocation and an administrative fine of $5,000.00 per day.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Not applicable to telehealth registrants.	
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Not applicable to telehealth registrants.	
(86) 1. Violating any provision of Chapters 459 and 456, F.S., or any rules adopted pursuant thereto. (Section 459.015,(1)(pp), F.S.)		
FIRST OFFENSE:	Reprimand and an administrative fine of $1,000.00.	Denial or revocation.
SECOND OFFENSE:	Probation and an administration fine of $5,000.00.	Denial or revocation.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand.	Denial or revocation.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension with a corrective action plan.	Denial or revocation.
2. Performing a pelvic examination on a patient without the written consent of the patient or the patient's legal representative executed specific to, and expressly identifying, the pelvic examination. (Sections 459.015(1)(pp), 456.51, F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	Denial or reprimand and an administrative fine of $2,500.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $2,500.00.	Denial or probation and an administrative fine of $5,000.00.
THIRD OFFENSE:	Probation and an administrative fine of $5,000.00.	Denial or revocation and an administrative fine of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Denial or suspension with a correction action plan.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Minimum six (6) months suspension with a corrective action plan	Denial or revocation.
(87) Intentionally implanting a patient or causing a patient to be implanted with a human embryo without the recipient's consent to the use of that human embryo, or inseminating a patient or causing a patient to be inseminated with the human reproductive material, as defined in Section 784.086, F.S., of a donor without the recipient's consent to the use of human reproductive material from that donor.		

(Section 456.072(1)(qq), F.S.		
FIRST OFFENSE:	Six (6) months probation and an administrative fine of $5,000.00.	Denial or one (1) year suspension and an administrative fine of $10,000.00.
SECOND OFFENSE:	One (1) year suspension and an administrative fine of $7,500.00.	Denial or revocation.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Six (6) months suspension with a corrective action plan.	Denial or one (1) year suspension with a corrective action plan.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	One (1) year suspension with a corrective action plan.	Denial or revocation.
(88) Implanting a patient or causing a patient to be implanted with a human embryo created with the human reproductive material, as defined in Section 784.086, F.S., of the licensee, or inseminating a patient or causing a patient to be inseminated with the human reproductive material of the licensee. (Section 459.015(1)(yy), F.S.)		
FIRST OFFENSE:	Revocation and an administrative fine of $10,000.00.	
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Denial or revocation.	
(89) Prescribing controlled substances in violation of Section 456.47(2)(c), F.S. (Section 456.47(2)(c), F.S.)		
FIRST OFFENSE:	Reprimand and a $5,000.00 fine.	Revocation.
SECOND OFFENSE:	Suspension and a $10,000.00 fine.	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand.	Revocation.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension with a corrective action plan.	Revocation or denial of licensure.
(90) Providing information indicating that a person has a disability or supporting a person's need for an emotional support animal under Section 760.27, F.S. without personal knowledge of the person's disability or disability-related need for the specific emotional support animal. (Section 456.072(1)(pp)		
FIRST OFFENSE:	Letter of concern and a fine of $500.00.	Probation and a fine of $1,000.00
SECOND OFFENSE:	Reprimand and a fine of $500.00.	Revocation and a fine of $1,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of Concern.	Suspension with a corrective action plan.
(91) Failure to display hyperlink on telehealth registrant's website. (Section 456.47(4)(c), F.S.		
FIRST OFFENSE:	Not applicable to physicians licensed under Chapter 459, F.S.	

FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern.	Suspension with a corrective action plan.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Reprimand.	Revocation.
(92) Opening an office in Florida or providing in-person healthcare services to patients in Florida. (Section 456.47(4)(f), F.S.)		
FIRST OFFENSE:	Not applicable to physicians licensed under Chapter 459, F.S.	
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Suspension with a corrective action plan.	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Revocation or denial of licensure.	
(93) Failure to report disciplinary action by another jurisdiction including pending disciplinary action. (Section 456.47(4)(d), F.S.		
FIRST OFFENSE:	Not applicable to physicians licensed under Chapter 459, F.S.	
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand	Revocation or denial of licensure.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension with a corrective action plan.	Revocation or denial of licensure.
(94) Failure to comply with parental consent requirements of Section 1014.06, F.S. (Section 456.072(1)(rr), F.S.)		
FIRST OFFENSE:	Letter of concern and a $1,000.00 fine.	Six (6) months probation and a $2,500.00 fine, or denial of licensure.
SECOND OFFENSE:	Reprimand and a $2,500.00 fine.	One (1) year probation and a $5,000.00 fine.
THIRD OFFENSE:	Six (6) month probation and a $5,000.00 fine.	Revocation and a $10,000.00 fine, or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand.	One (1) year suspension.
FOR TELEHEALTH REGISTRANTS SECOND OR SUBSEQUENT OFFENSE:	Six (6) month suspension with a corrective action plan.	Revocation, or denial of licensure.
(95) Being convicted or found guilty of, entering a plea, or committing or attempting, soliciting, or conspiring to commit an act that would constitute a violation of any of the offenses listed in Section 456.074(5), F.S. or similar offense in another jurisdiction. (Section 456.072(1)(ss), F.S.)		
FIRST OFFENSE:	Revocation and $1,000.00 fine, or denial of licensure.	Revocation and $5,000.00 fine, or denial of licensure.

SECOND OFFENSE:	Revocation and $5,000.00 fine, or denial of licensure.	Revocation and $10,000.00 fine, or denial of licensure.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Revocation, or denial of licensure.	
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Revocation, or denial of licensure.	
(96) Failing to identify through written notice, which may include the wearing of a name tag, or orally to a patient, the type of license under which the practitioner is practicing. (Section 456.072(1)(t), F.S.)		
FIRST OFFENSE:	Letter of concern and an administrative fine of $1,000.00.	One (1) year suspension to be followed by a period of probation and an administrative fine of $5,000.00.
SECOND OFFENSE:	Reprimand and an administrative fine of $5,000.00.	One (1) year suspension to be followed by a period of probation and an administrative fine of $10,000.00.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand.	One (1) year suspension with a corrective action plan.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension with a corrective action plan.	Revocation.
(97) With respect to making a personal injury protection claim as required by Section 627.736, F.S., intentionally submitting a claim, statement, or bill that has been "upcoded" as defined in Section 627.732, F.S. (Section 456.072(1)(ee), F.S.)		
FIRST OFFENSE:	One (1) year probation and a $10,000.00 fine, or denial of the license.	Revocation and a $10,000.00 fine, or denial of the license.
SECOND OFFENSE:	Suspension, to be followed by a period of probation, and a $10,000.00 fine.	Revocation and a $10,000.00 fine.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand, or denial of the license.	Revocation, or denial of the license.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension.	Revocation.
(98) With respect to making personal injury protection claim as required by Section 627.736, F.S., intentionally submitting a claim, statement, or bill for payment of services that were not rendered. (Section 456.072(1)(ff), F.S.)		
FIRST OFFENSE:	One (1) year probation and a $10,000.00 fine, or denial of the license.	Revocation and a $10,000.00 fine, or denial of the license.
SECOND OFFENSE:	Suspension, to be followed by a period	Revocation and a $10,000.00 fine.

	of probation, and a $10,000.00 fine.	
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Reprimand, or denial of the license.	Revocation, or denial of the license.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension.	Revocation.
(99) Violating Section 790.338(5), F.S. (Section 456.072(1)(nn), F.S.)		
FIRST OFFENSE:	Letter of concern and a $1,000.00 fine.	Probation and $5,000.00 fine
SECOND OFFENSE:	Probation and a $5,000.00 fine.	Suspension and a $10,000.00 fine.
FOR TELEHEALTH REGISTRANTS FIRST OFFENSE:	Letter of concern, or denial of the license.	Suspension with a corrective action plan, or denial of the license.
FOR TELEHEALTH REGISTRANTS SECOND OFFENSE:	Suspension with a corrective action plan.	Revocation.

Rulemaking Authority 456.079, 456.47(7), 459.015(5), 459.0138 FS. Law Implemented 381.986(3)(a), 456.072, 456.079, 456.47, 456.50, 459.015, 459.0138 FS. History–New 9-30-87, Amended 10-28-91, 1-12-93, Formerly 21R-19.002, 61F9-19.002, 59W-19.002, Amended 2-2-98, 2-11-01, 6-7-01, 2-26-02, 12-7-05, 11-14-06, 11-27-06, 5-10-10, 7-27-10, 11-10-11, 3-27-12, 7-3-12, 1-1-15, 11-27-16, 4-30-18, 8-9-18, 11-19-19, 2-12-20, 11-24-20, 4-18-21, 11-21-21, 3-22-23.

The 2022 Florida Statutes (including 2022 Special Session A and 2023 Special Session B)

458.331 Grounds for disciplinary action; action by the board and department.—

(1) The following acts constitute grounds for denial of a license or disciplinary action, as specified in s. 456.072(2):

(a) Attempting to obtain, obtaining, or renewing a license to practice medicine by bribery, by fraudulent misrepresentations, or through an error of the department or the board.

(b) Having a license or the authority to practice medicine revoked, suspended, or otherwise acted against, including the denial of licensure, by the licensing authority of any jurisdiction, including its agencies or subdivisions. The licensing authority's acceptance of a physician's relinquishment of a license, stipulation, consent order, or other settlement, offered in response to or in anticipation of the filing of administrative charges against the physician's license, shall be construed as action against the physician's license.

(c) Being convicted or found guilty of, or entering a plea of nolo contendere to, regardless of adjudication, a crime in any jurisdiction which directly relates to the practice of medicine or to the ability to practice medicine.

(d) False, deceptive, or misleading advertising.

(e) Failing to report to the department any person who the licensee knows is in violation of this chapter or of the rules of the department or the board. However, a person who the licensee knows is unable to practice medicine with reasonable skill and safety to patients by reason of illness or use of alcohol, drugs, narcotics, chemicals, or any other type of material, or as a result of a mental or physical condition, may be reported to a consultant operating an impaired practitioner program as described in s. 456.076 rather than to the department.

(f) Aiding, assisting, procuring, or advising any unlicensed person to practice medicine contrary to this chapter or to a rule of the department or the board.

(g) Failing to perform any statutory or legal obligation placed upon a licensed physician.

(h) Making or filing a report which the licensee knows to be false, intentionally or negligently failing to file a report or record required by state or federal law, willfully impeding or obstructing such filing or inducing another person to do so. Such reports or records shall include only those which are signed in the capacity as a licensed physician.

(i) Paying or receiving any commission, bonus, kickback, or rebate, or engaging in any split-fee arrangement in any form whatsoever with a physician, organization, agency, or person, either directly or indirectly, for patients referred to providers of health care goods and services, including, but not limited to, hospitals, nursing homes, clinical laboratories, ambulatory surgical centers, or pharmacies. The provisions of this paragraph shall not be construed to prevent a physician from receiving a fee for professional consultation services.

(j) Exercising influence within a patient-physician relationship for purposes of engaging a patient in sexual activity. A patient shall be presumed to be incapable of giving free, full, and informed consent to sexual activity with his or her physician.

(k) Making deceptive, untrue, or fraudulent representations in or related to the practice of medicine or employing a trick or scheme in the practice of medicine.

(l) Soliciting patients, either personally or through an agent, through the use of fraud, intimidation, undue influence, or a form of overreaching or vexatious conduct. A solicitation is any communication which directly or implicitly requests an immediate oral response from the recipient.

(m) Failing to keep legible, as defined by department rule in consultation with the board, medical records that identify the licensed physician or the physician extender and supervising physician by name and professional title who is or are responsible for rendering, ordering, supervising, or billing for each diagnostic or treatment procedure and that justify the course of treatment of the patient, including, but not limited to, patient histories; examination results; test results; records of drugs prescribed, dispensed, or administered; and reports of consultations and hospitalizations.

(n) Exercising influence on the patient or client in such a manner as to exploit the patient or client for financial gain of the licensee or of a third party, which shall include, but not be limited to, the promoting or selling of services, goods, appliances, or drugs.

(o) Promoting or advertising on any prescription form of a community pharmacy unless the form shall also state "This prescription may be filled at any pharmacy of your choice."

(p) Performing professional services which have not been duly authorized by the patient or client, or his or her legal representative, except as provided in s. 743.064, s. 766.103, or s. 768.13.

(q) Prescribing, dispensing, administering, mixing, or otherwise preparing a legend drug, including any controlled substance, other than in the course of the physician's professional practice. For the purposes of this paragraph, it shall be legally presumed that prescribing, dispensing, administering, mixing, or otherwise preparing legend drugs, including all controlled substances, inappropriately or in excessive or inappropriate quantities is not in the best interest of the patient and is not in the course of the physician's professional practice, without regard to his or her intent.

(r) Prescribing, dispensing, or administering any medicinal drug appearing on any schedule set forth in chapter 893 by the physician to himself or herself, except one prescribed, dispensed, or administered to the physician by another practitioner authorized to prescribe, dispense, or administer medicinal drugs.

(s) Being unable to practice medicine with reasonable skill and safety to patients by reason of illness or use of alcohol, drugs, narcotics, chemicals, or any other type of material or as a result of any mental or physical condition. In enforcing this paragraph, the department shall have, upon a finding of the State Surgeon General or the State Surgeon General's designee that probable cause exists to believe that the licensee is unable to practice medicine because of the reasons stated in this paragraph, the authority to issue an order to compel a licensee to submit to a mental or physical examination by physicians designated by the department. If the licensee refuses to comply with such order, the department's order directing such examination may be enforced by filing a petition for enforcement in the circuit court where the licensee resides or does business. The licensee against whom the petition is filed may not be named or identified by initials in any public court records or documents, and the proceedings shall be closed to the public. The department shall be entitled to the summary procedure provided in s. 51.011. A licensee or certificateholder affected under this paragraph shall at reasonable intervals be afforded an opportunity to demonstrate that he or she can resume the competent practice of medicine with reasonable skill and safety to patients.

(t) Notwithstanding s. 456.072(2) but as specified in s. 456.50(2):

1. Committing medical malpractice as defined in s. 456.50. The board shall give great weight to the provisions of s. 766.102 when enforcing this paragraph. Medical malpractice shall not be construed to require more than one instance, event, or act.

2. Committing gross medical malpractice.

3. Committing repeated medical malpractice as defined in s. 456.50. A person found by the board to have committed repeated medical malpractice based on s. 456.50 may not be licensed or continue to be licensed by this state to provide health care services as a medical doctor in this state.

Nothing in this paragraph shall be construed to require that a physician be incompetent to practice medicine in order to be disciplined pursuant to this paragraph. A recommended order by an administrative law judge or a final order of the board finding a violation under this paragraph shall specify whether the licensee was found to have committed "gross medical malpractice," "repeated medical malpractice," or "medical malpractice," or any combination thereof, and any publication by the board must so specify.

(u) Performing any procedure or prescribing any therapy which, by the prevailing standards of medical practice in the community, would constitute experimentation on a human subject, without first obtaining full, informed, and written consent.

(v) Practicing or offering to practice beyond the scope permitted by law or accepting and performing professional responsibilities which the licensee knows or has reason to know that he or she is not competent to perform. The board may establish by rule standards of practice and standards of care for particular practice settings, including, but not limited to, education and training, equipment and supplies, medications including anesthetics, assistance of and delegation to other personnel, transfer agreements, sterilization, records, performance of complex or multiple procedures, informed consent, and policy and procedure manuals.

(w) Delegating professional responsibilities to a person when the licensee delegating such responsibilities knows or has reason to know that such person is not qualified by training, experience, or licensure to perform them.

(x) Violating a lawful order of the board or department previously entered in a disciplinary hearing or failing to comply with a lawfully issued subpoena of the department.

(y) Conspiring with another licensee or with any other person to commit an act, or committing an act, which would tend to coerce, intimidate, or preclude another licensee from lawfully advertising his or her services.

(z) Procuring, or aiding or abetting in the procuring of, an unlawful termination of pregnancy.

(aa) Presigning blank prescription forms.

(bb) Prescribing any medicinal drug appearing on Schedule II in chapter 893 by the physician for office use.

(cc) Prescribing, ordering, dispensing, administering, supplying, selling, or giving any drug which is a Schedule II amphetamine or a Schedule II sympathomimetic amine drug or any compound thereof, pursuant to chapter 893, to or for any person except for:

1. The treatment of narcolepsy; hyperkinesis; behavioral syndrome characterized by the developmentally inappropriate symptoms of moderate to severe distractability, short attention span, hyperactivity, emotional lability, and impulsivity; or drug-induced brain dysfunction;

2. The differential diagnostic psychiatric evaluation of depression or the treatment of depression shown to be refractory to other therapeutic modalities; or

3. The clinical investigation of the effects of such drugs or compounds when an investigative protocol therefor is submitted to, reviewed, and approved by the board before such investigation is begun.

(dd) Failing to supervise adequately the activities of those physician assistants, paramedics, emergency medical technicians, advanced practice registered nurses, or anesthesiologist assistants acting under the supervision of the physician.

(ee) Prescribing, ordering, dispensing, administering, supplying, selling, or giving growth hormones, testosterone or its analogs, human chorionic gonadotropin (HCG), or other hormones for the purpose of muscle building or to enhance athletic performance. For the purposes of this subsection, the term "muscle building" does not include the treatment of injured muscle. A prescription written for the drug products listed above may be dispensed by the pharmacist with the presumption that the prescription is for legitimate medical use.

(ff) Prescribing, ordering, dispensing, administering, supplying, selling, or giving amygdalin (laetrile) to any person.

(gg) Misrepresenting or concealing a material fact at any time during any phase of a licensing or disciplinary process or procedure.

(hh) Improperly interfering with an investigation or with any disciplinary proceeding.

(ii) Failing to report to the department any licensee under this chapter or under chapter 459 who the physician or physician assistant knows has violated the grounds for disciplinary action set out in the law under which that person is licensed and who provides health care services in a facility licensed under chapter 395, or a health maintenance organization certificated under part I of chapter 641, in which the physician or physician assistant also provides services.

(jj) Being found by any court in this state to have provided corroborating written medical expert opinion attached to any statutorily required notice of claim or intent or to any statutorily required response rejecting a claim, without reasonable investigation.

(kk) Failing to report to the board, in writing, within 30 days if action as defined in paragraph (b) has been taken against one's license to practice medicine in another state, territory, or country.

(ll) Advertising or holding oneself out as a board-certified specialist, if not qualified under s. 458.3312, in violation of this chapter.

(mm) Failing to comply with the requirements of ss. 381.026 and 381.0261 to provide patients with information about their patient rights and how to file a patient complaint.

(nn) Violating any provision of this chapter or chapter 456, or any rules adopted pursuant thereto.

(oo) Providing deceptive or fraudulent expert witness testimony related to the practice of medicine.

(pp) Applicable to a licensee who serves as the designated physician of a pain-management clinic as defined in s. 458.3265 or s. 459.0137:

1. Registering a pain-management clinic through misrepresentation or fraud;

2. Procuring, or attempting to procure, the registration of a pain-management clinic for any other person by making, or causing to be made, any false representation;

3. Failing to comply with any requirement of chapter 499, the Florida Drug and Cosmetic Act; 21 U.S.C. ss. 301-392, the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. ss. 821 et seq., the Drug Abuse Prevention and Control Act; or chapter 893, the Florida Comprehensive Drug Abuse Prevention and Control Act;

4. Being convicted or found guilty of, regardless of adjudication to, a felony or any other crime involving moral turpitude, fraud, dishonesty, or deceit in any jurisdiction of the courts of this state, of any other state, or of the United States;

5. Being convicted of, or disciplined by a regulatory agency of the Federal Government or a regulatory agency of another state for, any offense that would constitute a violation of this chapter;

6. Being convicted of, or entering a plea of guilty or nolo contendere to, regardless of adjudication, a crime in any jurisdiction of the courts of this state, of any other state, or of the United States which relates to the practice of, or the ability to practice, a licensed health care profession;

7. Being convicted of, or entering a plea of guilty or nolo contendere to, regardless of adjudication, a crime in any jurisdiction of the courts of this state, of any other state, or of the United States which relates to health care fraud;

8. Dispensing any medicinal drug based upon a communication that purports to be a prescription as defined in s. 465.003 or s. 893.02 if the dispensing practitioner knows or has reason to believe that the purported prescription is not based upon a valid practitioner-patient relationship; or

9. Failing to timely notify the board of the date of his or her termination from a pain-management clinic as required by s. 458.3265(3).

(qq) Failing to timely notify the department of the theft of prescription blanks from a pain-management clinic or a breach of a physician's electronic prescribing software within 24 hours as required by s. 458.3265(3).

(rr) Promoting or advertising through any communication media the use, sale, or dispensing of any controlled substance appearing on any schedule in chapter 893.

(ss) Dispensing a controlled substance listed in Schedule II or Schedule III in violation of s. 465.0276.

(tt) Willfully failing to comply with s. 627.64194 or s. 641.513 with such frequency as to indicate a general business practice.

(uu) Issuing a physician certification, as defined in s. 381.986, in a manner out of compliance with the requirements of that section and rules adopted thereunder.

(vv) Performing a liposuction procedure in which more than 1,000 cubic centimeters of supernatant fat is removed, a Level II office surgery, or a Level III office surgery in an office that is not registered with the department pursuant to s. 458.328 or s. 459.0138.

(ww) Implanting a patient or causing a patient to be implanted with a human embryo created with the human reproductive material, as defined in s. 784.086, of the licensee, or inseminating a patient or causing a patient to be inseminated with the human reproductive material of the licensee.

(2) The board may enter an order denying licensure or imposing any of the penalties in s. 456.072(2) against any applicant for licensure or licensee who is found guilty of violating any provision of subsection (1) of this section or who is found guilty of violating any provision of s. 456.072(1). In determining what action is appropriate, the board must first consider what sanctions are necessary to protect the public or to compensate the patient. Only after those sanctions have been imposed may the disciplining authority consider and include in the order requirements designed to rehabilitate the physician. All costs associated with compliance with orders issued under this subsection are the obligation of the physician.

(3) In any administrative action against a physician which does not involve revocation or suspension of license, the division shall have the burden, by the greater weight of the evidence, to establish the existence of grounds for disciplinary action. The division shall establish grounds for revocation or suspension of license by clear and convincing evidence.

(4) The board shall not reinstate the license of a physician, or cause a license to be issued to a person it deems or has deemed unqualified, until such time as it is satisfied that he or she has complied with all the terms and conditions set forth in the final order and that such person is capable of safely engaging in the practice of medicine. However, the board may not issue a license to, or reinstate the license of, any medical doctor found by the board to have committed repeated medical malpractice based on s. 456.50, regardless of the extent to which the licensee or prospective licensee has complied with all terms and conditions set forth in the final order and is capable of safely engaging in the practice of medicine.

(5) The board shall by rule establish guidelines for the disposition of disciplinary cases involving specific types of violations. Such guidelines may include minimum and maximum fines, periods of supervision or probation, or conditions of probation or reissuance of a license. "Gross medical malpractice," "repeated medical malpractice," and "medical malpractice," under paragraph (1)(t) shall each be considered distinct types of violations requiring specific individual guidelines.

(6) Upon the department's receipt from an insurer or self-insurer of a report of a closed claim against a physician pursuant to s. 627.912 or from a health care practitioner of a report pursuant to s. 456.049, or upon the receipt from a claimant of a presuit notice against a physician pursuant to s. 766.106, the department shall review each report and determine whether it potentially involved conduct by a licensee that is subject to disciplinary action, in which case the provisions of s. 456.073 shall apply. However, if it is reported that a physician has had three or more claims with indemnities exceeding $50,000 each within the previous 5-year period, the department shall investigate the occurrences upon which the claims were based and determine if action by the department against the physician is warranted.

(7) Upon the department's receipt from the Agency for Health Care Administration pursuant to s. 395.0197 of the name of a physician whose conduct may constitute grounds for disciplinary action by the department, the department shall investigate the occurrences upon which the report was based and determine if action by the department against the physician is warranted.

(8) If any physician regulated by the Division of Medical Quality Assurance is guilty of such unprofessional conduct, negligence, or mental or physical incapacity or impairment that the division determines that the physician is unable to practice with reasonable skill and safety and presents a danger

to patients, the division shall be authorized to maintain an action in circuit court enjoining such physician from providing medical services to the public until the physician demonstrates the ability to practice with reasonable skill and safety and without danger to patients.

(9) When an investigation of a physician is undertaken, the department shall promptly furnish to the physician or the physician's attorney a copy of the complaint or document which resulted in the initiation of the investigation. For purposes of this subsection, such documents include, but are not limited to: the pertinent portions of an annual report submitted to the department pursuant to s. 395.0197(6); a report of an adverse incident which is provided to the department pursuant to s. 395.0197; a report of peer review disciplinary action submitted to the department pursuant to s. 395.0193(4) or s. 458.337, providing that the investigations, proceedings, and records relating to such peer review disciplinary action shall continue to retain their privileged status even as to the licensee who is the subject of the investigation, as provided by ss. 395.0193(8) and 458.337(3); a report of a closed claim submitted pursuant to s. 627.912; a presuit notice submitted pursuant to s. 766.106(2); and a petition brought under the Florida Birth-Related Neurological Injury Compensation Plan, pursuant to s. 766.305(2). The physician may submit a written response to the information contained in the complaint or document which resulted in the initiation of the investigation within 45 days after service to the physician of the complaint or document. The physician's written response shall be considered by the probable cause panel.

(10) A probable cause panel convened to consider disciplinary action against a physician assistant alleged to have violated s. 456.072 or this section must include one physician assistant. The physician assistant must hold a valid license to practice as a physician assistant in this state and be appointed to the panel by the Council of Physician Assistants. The physician assistant may hear only cases involving disciplinary actions against a physician assistant. If the appointed physician assistant is not present at the disciplinary hearing, the panel may consider the matter and vote on the case in the absence of the physician assistant. The training requirements set forth in s. 458.307(4) do not apply to the appointed physician assistant. Rules need not be adopted to implement this subsection.

(11) The purpose of this section is to facilitate uniform discipline for those acts made punishable under this section and, to this end, a reference to this section constitutes a general reference under the doctrine of incorporation by reference.

History.—ss. 1, 8, ch. 79-302; s. 2, ch. 80-354; s. 297, ch. 81-259; ss. 2, 3, ch. 81-318; ss. 2, 4, ch. 82-32; s. 15, ch. 83-329; s. 1, ch. 85-6; s. 4, ch. 85-175; ss. 18, 25, 26, ch. 86-245; s. 25, ch. 88-1; s. 18, ch. 89-275; s. 16, ch. 89-283; ss. 11, 72, ch. 89-374; s. 2, ch. 90-44; s. 4, ch. 90-60; s. 26, ch. 90-228; s. 60, ch. 91-220; s. 4, ch. 91-429; s. 39, ch. 92-149; s. 1, ch. 92-178; s. 83, ch. 92-289; s. 218, ch. 96-410; s. 1090, ch. 97-103; s. 106, ch. 97-261; s. 23, ch. 97-264; s. 37, ch. 98-89; s. 46, ch. 98-166; s. 222, ch. 99-8; s. 99, ch. 99-397; s. 105, ch. 2000-160; ss. 21, 76, ch. 2001-277; s. 25, ch. 2003-416; s. 2, ch. 2004-303; s. 3, ch. 2005-240; s. 3, ch. 2005-266; s. 1, ch. 2006-242; s. 73, ch. 2008-6; s. 6, ch. 2010-211; s. 6, ch. 2011-141; s. 2, ch. 2011-233; s. 2, ch. 2013-166; s. 17, ch. 2016-145; s. 9, ch. 2016-222; s. 22, ch. 2016-224; s. 8, ch. 2017-41; ss. 1, 4, ch. 2017-232; s. 14, ch. 2018-13; s. 50, ch. 2018-106; s. 6, ch. 2019-112; s. 4, ch. 2019-130; s. 4, ch. 2020-31; s. 14, ch. 2022-35.

[1]**Note.**—Section 1, ch. 2017-232, provides that "[i]t is the intent of the Legislature to implement s. 29, Article X of the State Constitution by creating a unified regulatory structure. If s. 29, Article X of the State Constitution is amended or a constitutional amendment related to cannabis or marijuana is adopted, this act shall expire 6 months after the effective date of such amendment." If such amendment or adoption takes place, paragraph (1)(uu), as created by s. 4, ch. 2017-232, is repealed.

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Title XXXII REGULATION OF PROFESSIONS AND OCCUPATIONS

Chapter 459 OSTEOPATHIC MEDICINE

SECTION 015 Grounds for disciplinary action; action by the board and department.

459.015 Grounds for disciplinary action; action by the board and department.—
(1) The following acts constitute grounds for denial of a license or disciplinary action, as specified in s. 456.072(2):
(a) Attempting to obtain, obtaining, or renewing a license to practice osteopathic medicine or a certificate issued under this chapter by bribery, by fraudulent misrepresentations, or through an error of the department or the board.
(b) Having a license or the authority to practice osteopathic medicine revoked, suspended, or otherwise acted against, including the denial of licensure, by the licensing authority of any jurisdiction, including its agencies or subdivisions. The licensing authority's acceptance of a physician's relinquishment of license, stipulation, consent order, or other settlement offered in response to or in anticipation of the filing of administrative charges against the physician shall be construed as action against the physician's license.
(c) Being convicted or found guilty, regardless of adjudication, of a crime in any jurisdiction which directly relates to the practice of osteopathic medicine or to the ability to practice osteopathic medicine. A plea of nolo contendere shall create a rebuttable presumption of guilt to the underlying criminal charges.
(d) False, deceptive, or misleading advertising.
(e) Failing to report to the department or the department's impaired professional consultant any person who the licensee or certificateholder knows is in violation of this chapter or of the rules of the department or the board. However, a person who the licensee knows is unable to practice osteopathic medicine with reasonable skill and safety to patients by reason of illness or use of alcohol, drugs, narcotics, chemicals, or any other type of material, or as a result of a mental or physical condition, may be reported to a consultant operating an impaired practitioner program as described in s. 456.076 rather than to the department.
(f) Aiding, assisting, procuring, or advising any unlicensed person to practice osteopathic medicine contrary to this chapter or to a rule of the department or the board.
(g) Failing to perform any statutory or legal obligation placed upon a licensed osteopathic physician.
(h) Giving false testimony in the course of any legal or administrative proceedings relating to the practice of medicine or the delivery of health care services.
(i) Making or filing a report which the licensee knows to be false, intentionally or negligently failing to file a report or record required by state or federal law, willfully impeding or obstructing such filing, or inducing another person to do so. Such reports or records shall include only those which are signed in the capacity as a licensed osteopathic physician.
(j) Paying or receiving any commission, bonus, kickback, or rebate, or engaging in any split-fee arrangement in any form whatsoever with a physician, organization, agency, person, partnership, firm, corporation, or other business entity, for patients referred to providers of health care goods and services, including, but not limited to, hospitals, nursing homes, clinical laboratories, ambulatory surgical centers, or pharmacies. The provisions of this paragraph shall not be construed to prevent an osteopathic physician from receiving a fee for professional consultation services.

sexual activity with his or her physician.
(m) Making deceptive, untrue, or fraudulent representations in or related to the practice of osteopathic medicine or employing a trick or scheme in the practice of osteopathic medicine.
(n) Soliciting patients, either personally or through an agent, through the use of fraud, intimidation, undue influence, or forms of overreaching or vexatious conduct. A solicitation is any communication which directly or implicitly requests an immediate oral response from the recipient.
(o) Failing to keep legible, as defined by department rule in consultation with the board, medical records that identify the licensed osteopathic physician or the osteopathic physician extender and supervising osteopathic physician by name and professional title who is or are responsible for rendering, ordering, supervising, or billing for each diagnostic or treatment procedure and that justify the course of treatment of the patient, including, but not limited to, patient histories; examination results; test results; records of drugs prescribed, dispensed, or administered; and reports of consultations and hospitalizations.
(p) Fraudulently altering or destroying records relating to patient care or treatment, including, but not limited to, patient histories, examination results, and test results.
(q) Exercising influence on the patient or client in such a manner as to exploit the patient or client for financial gain of the licensee or of a third party which shall include, but not be limited to, the promotion or sale of services, goods, appliances, or drugs.
(r) Promoting or advertising on any prescription form of a community pharmacy, unless the form shall also state “This prescription may be filled at any pharmacy of your choice.”
(s) Performing professional services which have not been duly authorized by the patient or client or his or her legal representative except as provided in s. **743.064**, s. **766.103**, or s. **768.13**.
(t) Prescribing, dispensing, administering, supplying, selling, giving, mixing, or otherwise preparing a legend drug, including all controlled substances, other than in the course of the osteopathic physician’s professional practice. For the purposes of this paragraph, it shall be legally presumed that prescribing, dispensing, administering, supplying, selling, giving, mixing, or otherwise preparing legend drugs, including all controlled substances, inappropriately or in excessive or inappropriate quantities is not in the best interest of the patient and is not in the course of the osteopathic physician’s professional practice, without regard to his or her intent.
(u) Prescribing or dispensing any medicinal drug appearing on any schedule set forth in chapter 893 by the osteopathic physician for himself or herself or administering any such drug by the osteopathic physician to himself or herself unless such drug is prescribed for the osteopathic physician by another practitioner authorized to prescribe medicinal drugs.
(v) Prescribing, ordering, dispensing, administering, supplying, selling, or giving amygdalin (laetrile) to any person.
(w) Being unable to practice osteopathic medicine with reasonable skill and safety to patients by reason of illness or use of alcohol, drugs, narcotics, chemicals, or any other type of material or as a result of any mental or physical condition. In enforcing this paragraph, the department shall, upon a finding of the State Surgeon General or the State Surgeon General’s designee that probable cause exists to believe that the licensee is unable to practice medicine because of the reasons stated in this paragraph, have the authority to issue an order to compel a licensee to submit to a mental or physical examination by physicians designated by the department. If the licensee refuses to comply with such order, the department’s order directing such examination may be enforced by filing a petition for enforcement in the circuit court where the licensee resides or does business. The licensee against whom the petition is filed shall not be named or identified by initials in any public court records or documents, and the proceedings shall be closed to the public. The department shall be entitled to the summary procedure provided in s. **51.011**. A licensee or certificateholder affected under this paragraph shall at reasonable intervals be afforded an opportunity to demonstrate that he or she can resume the competent practice of medicine with reasonable skill and safety to patients.
(x) Notwithstanding s. **456.072**(2) but as specified in s. **456.50**(2):
1. Committing medical malpractice as defined in s. **456.50**. The board shall give great weight to the provisions of s. **766.102** when enforcing this paragraph. Medical malpractice shall not be construed to

licensed by this state to provide health care services as a medical doctor in this state.

Nothing in this paragraph shall be construed to require that an osteopathic physician be incompetent to practice osteopathic medicine in order to be disciplined pursuant to this paragraph. A recommended order by an administrative law judge or a final order of the board finding a violation under this paragraph shall specify whether the licensee was found to have committed “gross medical malpractice,” “repeated medical malpractice,” or “medical malpractice,” or any combination thereof, and any publication by the board shall so specify.

(y) Performing any procedure or prescribing any therapy which, by the prevailing standards of medical practice in the community, would constitute experimentation on human subjects, without first obtaining full, informed, and written consent.

(z) Practicing or offering to practice beyond the scope permitted by law or accepting and performing professional responsibilities which the licensee knows or has reason to know that he or she is not competent to perform. The board may establish by rule standards of practice and standards of care for particular practice settings, including, but not limited to, education and training, equipment and supplies, medications including anesthetics, assistance of and delegation to other personnel, transfer agreements, sterilization, records, performance of complex or multiple procedures, informed consent, and policy and procedure manuals.

(aa) Delegating professional responsibilities to a person when the licensee delegating such responsibilities knows or has reason to know that such person is not qualified by training, experience, or licensure to perform them.

(bb) Violating a lawful order of the board or department previously entered in a disciplinary hearing or failing to comply with a lawfully issued subpoena of the board or department.

(cc) Conspiring with another licensee or with any other person to commit an act, or committing an act, which would tend to coerce, intimidate, or preclude another licensee from lawfully advertising his or her services.

(dd) Procuring, or aiding or abetting in the procuring of, an unlawful termination of pregnancy.

(ee) Presigning blank prescription forms.

(ff) Prescribing any medicinal drug appearing on Schedule II in chapter 893 by the osteopathic physician for office use.

(gg) Prescribing, ordering, dispensing, administering, supplying, selling, or giving any drug which is a Schedule II amphetamine or Schedule II sympathomimetic amine drug or any compound thereof, pursuant to chapter 893, to or for any person except for:

1. The treatment of narcolepsy; hyperkinesis; behavioral syndrome characterized by the developmentally inappropriate symptoms of moderate to severe distractability, short attention span, hyperactivity, emotional lability, and impulsivity; or drug-induced brain dysfunction;
2. The differential diagnostic psychiatric evaluation of depression or the treatment of depression shown to be refractory to other therapeutic modalities; or
3. The clinical investigation of the effects of such drugs or compounds when an investigative protocol therefor is submitted to, reviewed, and approved by the board before such investigation is begun.

(hh) Failing to supervise adequately the activities of those physician assistants, paramedics, emergency medical technicians, advanced practice registered nurses, anesthesiologist assistants, or other persons acting under the supervision of the osteopathic physician.

(ii) Prescribing, ordering, dispensing, administering, supplying, selling, or giving growth hormones, testosterone or its analogs, human chorionic gonadotropin (HCG), or other hormones for the purpose of muscle building or to enhance athletic performance. For the purposes of this subsection, the term “muscle building” does not include the treatment of injured muscle. A prescription written for the drug products listed above may be dispensed by the pharmacist with the presumption that the prescription is for legitimate medical use.

(jj) Misrepresenting or concealing a material fact at any time during any phase of a licensing or disciplinary process or procedure.

(kk) Improperly interfering with an investigation or with any disciplinary proceeding.

licensed under chapter 395, or a health maintenance organization certificated under part I of chapter 641, in which the osteopathic physician or physician assistant also provides services.
(mm) Being found by any court in this state to have provided corroborating written medical expert opinion attached to any statutorily required notice of claim or intent or to any statutorily required response rejecting a claim, without reasonable investigation.
(nn) Advertising or holding oneself out as a board-certified specialist in violation of this chapter.
(oo) Failing to comply with the requirements of ss. 381.026 and 381.0261 to provide patients with information about their patient rights and how to file a patient complaint.
(pp) Violating any provision of this chapter or chapter 456, or any rules adopted pursuant thereto.
(qq) Providing deceptive or fraudulent expert witness testimony related to the practice of osteopathic medicine.
(rr) Applicable to a licensee who serves as the designated physician of a pain-management clinic as defined in s. 458.3265 or s. 459.0137:
1. Registering a pain-management clinic through misrepresentation or fraud;
2. Procuring, or attempting to procure, the registration of a pain-management clinic for any other person by making, or causing to be made, any false representation;
3. Failing to comply with any requirement of chapter 499, the Florida Drug and Cosmetic Act; 21 U.S.C. ss. 301-392, the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. ss. 821 et seq., the Drug Abuse Prevention and Control Act; or chapter 893, the Florida Comprehensive Drug Abuse Prevention and Control Act;
4. Being convicted or found guilty of, regardless of adjudication to, a felony or any other crime involving moral turpitude, fraud, dishonesty, or deceit in any jurisdiction of the courts of this state, of any other state, or of the United States;
5. Being convicted of, or disciplined by a regulatory agency of the Federal Government or a regulatory agency of another state for, any offense that would constitute a violation of this chapter;
6. Being convicted of, or entering a plea of guilty or nolo contendere to, regardless of adjudication, a crime in any jurisdiction of the courts of this state, of any other state, or of the United States which relates to the practice of, or the ability to practice, a licensed health care profession;
7. Being convicted of, or entering a plea of guilty or nolo contendere to, regardless of adjudication, a crime in any jurisdiction of the courts of this state, of any other state, or of the United States which relates to health care fraud;
8. Dispensing any medicinal drug based upon a communication that purports to be a prescription as defined in s. 465.003 or s. 893.02 if the dispensing practitioner knows or has reason to believe that the purported prescription is not based upon a valid practitioner-patient relationship; or
9. Failing to timely notify the board of the date of his or her termination from a pain-management clinic as required by s. 459.0137(3).
(ss) Failing to timely notify the department of the theft of prescription blanks from a pain-management clinic or a breach of an osteopathic physician's electronic prescribing software within 24 hours as required by s. 459.0137(3).
(tt) Promoting or advertising through any communication media the use, sale, or dispensing of any controlled substance appearing on any schedule in chapter 893.
(uu) Dispensing a controlled substance listed in Schedule II or Schedule III in violation of s. 465.0276.
(vv) Willfully failing to comply with s. 627.64194 or s. 641.513 with such frequency as to indicate a general business practice.
[1](ww) Issuing a physician certification, as defined in s. 381.986, in a manner not in compliance with the requirements of that section and rules adopted thereunder.
(xx) Performing a liposuction procedure in which more than 1,000 cubic centimeters of supernatant fat is removed, a Level II office surgery, or a Level III office surgery in an office that is not registered with the department pursuant to s. 458.328 or s. 459.0138.
(yy) Implanting a patient or causing a patient to be implanted with a human embryo created with the human reproductive material, as defined in s. 784.086, of the licensee, or inseminating a patient or causing a patient to be inseminated with the human reproductive material of the licensee.

to compensate the patient. Only after those sanctions have been imposed may the disciplining authority consider and include in the order requirements designed to rehabilitate the physician. All costs associated with compliance with orders issued under this subsection are the obligation of the physician.

(3) In any administrative action against a physician which does not involve revocation or suspension of license, the division shall have the burden, by the greater weight of the evidence, to establish the existence of grounds for disciplinary action. The division shall establish grounds for revocation or suspension of license by clear and convincing evidence.

(4) The board shall not reinstate the license or certificate of an osteopathic physician, or cause a license or certificate to be issued to a person it has deemed unqualified, until such time as it is satisfied that he or she has complied with all the terms and conditions set forth in the final order and that such person is capable of safely engaging in the practice of osteopathic medicine. However, the board may not issue a license to, or reinstate the license of, any medical doctor found by the board to have committed repeated medical malpractice based on s. **456.50**, regardless of the extent to which the licensee or prospective licensee has complied with all terms and conditions set forth in the final order and is capable of safely engaging in the practice of osteopathic medicine.

(5) The board shall, by rule, establish comprehensive guidelines for the disposition of disciplinary cases involving specific types of violations. Such guidelines shall establish offenses and circumstances for which revocation will be presumed to be appropriate, as well as offenses and circumstances for which suspension for particular periods of time will be presumed to be appropriate. The guidelines shall also establish minimum and maximum fines, periods of supervision or probation, or conditions of probation and conditions for reissuance of a license with respect to particular circumstances and offenses. “Gross medical malpractice,” “repeated medical malpractice,” and “medical malpractice,” under paragraph (1)(x) shall each be considered distinct types of violations requiring specific individual guidelines.

(6) Upon the department’s receipt from an insurer or self-insurer of a report of a closed claim against an osteopathic physician pursuant to s. **627.912** or from a health care practitioner of a report pursuant to s. **456.049**, or upon the receipt from a claimant of a presuit notice against an osteopathic physician pursuant to s. **766.106**, the department shall review each report and determine whether it potentially involved conduct by a licensee that is subject to disciplinary action, in which case the provisions of s. **456.073** shall apply. However, if it is reported that an osteopathic physician has had three or more claims with indemnities exceeding $50,000 each within the previous 5-year period, the department shall investigate the occurrences upon which the claims were based and determine if action by the department against the osteopathic physician is warranted.

(7) Upon the department’s receipt from the Agency for Health Care Administration pursuant to s. **395.0197** of the name of an osteopathic physician whose conduct may constitute grounds for disciplinary action by the department, the department shall investigate the occurrences upon which the report was based and determine if action by the department against the osteopathic physician is warranted.

(8) If any osteopathic physician regulated by the Division of Medical Quality Assurance is guilty of such unprofessional conduct, negligence, or mental or physical incapacity or impairment that the division determines that the osteopathic physician is unable to practice with reasonable skill and safety and presents a danger to patients, the division shall be authorized to maintain an action in circuit court enjoining such osteopathic physician from providing medical services to the public until the osteopathic physician demonstrates the ability to practice with reasonable skill and safety and without danger to patients.

(9) When an investigation of an osteopathic physician is undertaken, the department shall promptly furnish to the osteopathic physician or his or her attorney a copy of the complaint or document which resulted in the initiation of the investigation. For purposes of this subsection, such documents include, but are not limited to: the pertinent portions of an annual report submitted to the department pursuant to s. **395.0197**(6); a report of an adverse incident which is provided to the department pursuant to s. **395.0197**; a report of peer review disciplinary action submitted to the department pursuant to s. **395.0193**(4) or s. **459.016**, provided that the investigations, proceedings, and records relating to such

766.305(2). The osteopathic physician may submit a written response to the information contained in the complaint or document which resulted in the initiation of the investigation within 45 days after service to the osteopathic physician of the complaint or document. The osteopathic physician's written response shall be considered by the probable cause panel.

(10) A probable cause panel convened to consider disciplinary action against a physician assistant alleged to have violated s. 456.072 or this section must include one physician assistant. The physician assistant must hold a valid license to practice as a physician assistant in this state and be appointed to the panel by the Council of Physician Assistants. The physician assistant may hear only cases involving disciplinary actions against a physician assistant. If the appointed physician assistant is not present at the disciplinary hearing, the panel may consider the matter and vote on the case in the absence of the physician assistant. The training requirements set forth in s. 458.307(4) do not apply to the appointed physician assistant. Rules need not be adopted to implement this subsection.

(11) The purpose of this section is to facilitate uniform discipline for those acts made punishable under this section and, to this end, a reference to this section constitutes a general reference under the doctrine of incorporation by reference.

History.—ss. 1, 6, ch. 79-230; s. 3, ch. 80-354; s. 305, ch. 81-259; ss. 2, 3, ch. 81-318; s. 19, ch. 83-329; s. 2, ch. 85-6; s. 5, ch. 85-175; ss. 16, 27, 29, ch. 86-290; s. 54, ch. 87-225; s. 35, ch. 88-1; s. 13, ch. 88-277; s. 3, ch. 90-44; s. 27, ch. 90-228; s. 3, ch. 90-254; s. 63, ch. 91-220; s. 4, ch. 91-429; s. 40, ch. 92-149; s. 2, ch. 92-178; s. 84, ch. 92-289; s. 29, ch. 95-144; s. 221, ch. 96-410; s. 1097, ch. 97-103; s. 107, ch. 97-261; s. 33, ch. 97-264; s. 38, ch. 98-89; s. 52, ch. 98-166; s. 223, ch. 99-8; s. 103, ch. 99-397; s. 111, ch. 2000-160; ss. 25, 77, ch. 2001-277; s. 27, ch. 2003-416; s. 4, ch. 2004-303; s. 4, ch. 2005-240; s. 4, ch. 2005-266; s. 2, ch. 2006-242; s. 77, ch. 2008-6; s. 10, ch. 2010-211; s. 9, ch. 2011-141; s. 5, ch. 2011-233; s. 3, ch. 2013-166; s. 18, ch. 2016-145; s. 10, ch. 2016-222; s. 22, ch. 2016-224; s. 9, ch. 2017-41; ss. 1, 5, ch. 2017-232; s. 15, ch. 2018-13; s. 53, ch. 2018-106; s. 8, ch. 2019-112; s. 7, ch. 2019-130; s. 5, ch. 2020-31; s. 15, ch. 2022-35.

[1]Note.—Section 1, ch. 2017-232, provides that "[i]t is the intent of the Legislature to implement s. 29, Article X of the State Constitution by creating a unified regulatory structure. If s. 29, Article X of the State Constitution is amended or a constitutional amendment related to cannabis or marijuana is adopted, this act shall expire 6 months after the effective date of such amendment." If such amendment or adoption takes place, paragraph (1)(ww), as created by s. 5, ch. 2017-232, is repealed.

FLORIDA BOARD OF MEDICINE AND FLORIDA BOARD OF OSTEOPATHIC MEDICINE APPROVED INFORMED CONSENT FORM FOR CATARACT OPERATION WITH OR WITHOUT IMPLANTATION OF INTRAOCULAR LENS

DOES THE PATIENT NEED OR WANT A TRANSLATOR, INTERPRETOR OR READER?
YES_____NO_____

TO THE PATIENT: You have the right, as a patient, to be informed about your cataract condition and the recommended surgical procedure to be used, so that you may make the decision whether or not to undergo the cataract surgery, after knowing the risks, possible complications, and alternatives involved. This disclosure is not meant to scare or alarm you; it is simply an effort to make you better informed so that you may give or withhold your consent to cataract surgery and should reflect the information provided by your eye surgeon. If you have any questions or do not understand the information, please discuss the procedure with your eye surgeon prior to signing.

WHAT IS A CATARACT, AND HOW IS IT TREATED?

The lens in the eye can become cloudy and hard, a condition known as a cataract. Cataracts can develop from normal aging, from an eye injury, various medical conditions or if you have taken certain medications such as steroids. Cataracts may cause blurred vision, dulled vision, sensitivity to light and glare, and/or ghost images. If the cataract changes vision so much that it interferes with your daily life, the cataract may need to be removed to try to improve your vision. Surgery is the only way to remove a cataract. You can decide to postpone surgery or not to have the cataract removed.

ALTERNATIVE TREATMENTS:

I understand that I may decide not to have a cataract operation, at all. However, if I do not have the cataract surgery, I understand my vision loss from the cataract usually will continue to get worse. Corrective lenses, eyeglasses, or contact lenses will not improve my vision or reverse the worsening of the cataract.

HOW WILL REMOVING THE CATARACT AFFECT MY VISION?

The goal of cataract surgery is to correct the decreased vision that was caused by the cataract. During the surgery, the ophthalmologist (eye surgeon) removes the cataract and may place in a new artificial lens called an intraocular lens or IOL. Cataract surgery will **not** correct other causes of decreased vision, such as glaucoma, optic nerve or retinal problems, diabetes, age- related macular degeneration, or dry eye. In order to obtain the best possible vision, many people still need to wear glasses or contact lenses after cataract surgery for either near and/or distance vision, for some activities, or in low light.

WHAT ARE THE TYPES OF INTRA-OCULAR-LENSES (IOL) THAT ARE AVAILABLE FOR ME?

Your ophthalmologist will help you decide on the type of IOL that will replace your cloudy lens. There are IOLs available to treat nearsightedness (myopia), farsightedness (hyperopia), and astigmatism. IOLs usually provide either near or distance vision-- these single focus lenses are called **monofocal IOLs**. Some more recently developed IOLs may provide for near, intermediate, and distance vision-- these multiple focus lenses are called **multifocal IOLs**. Lenses that have some focusing power are called **accommodative IOLs**. IOLs that treat astigmatism are called **toric IOLs**.

You can also have one eye corrected for near vision, and the other for distance vision, a choice called **monovision**. With monovision the implanted IOLs have two different powers, one for near vision in one eye, and one for distance vision in the other eye. Monovision allows for near and distance vision but can decrease depth perception. Although many patients adjust well to monovision, some may find it uncomfortable, which may require compensating glasses, contact lenses or another operation to change the IOL.

No IOL is perfect, and often glasses or contact lenses are needed for certain activities even if you have chosen a special IOL lens.

DO I HAVE ASTIGMATISM IN ADDITION TO MY CATARACT? ARE THERE TREATMENTS FOR IT?

Patients with nearsightedness and farsightedness may also have astigmatism. Astigmatism is caused by an irregularly shaped cornea; instead of being round like a basketball, the cornea is shaped like an American style football. This can make your vision blurry. In addition to toric IOLs, astigmatism can be reduced by glasses, contact lenses, and refractive surgery (Laser assisted in situ keratomileusis [LASIK] or Photorefractive keratectomy [PRK]).

There is also a procedure called a limbal relaxing incision (LRI), which can be done at the same time as the cataract operation, or as a separate procedure. A LRI is a small cut or incision the ophthalmologist makes into your cornea to make its shape more round. Astigmatic Keratotomy (AK) is a similar procedure that involves a smaller, more central incision in the cornea than the LRI.

Any attempt at astigmatism reduction could result in over- or under-correction, in which case glasses, contact lenses, or another procedure may be needed. None of the methods of reducing astigmatism are perfect or completely predictable, but all are designed to help reduce the amount

of astigmatism present.

WHAT ARE THE RECOGNIZED RISKS OF CATARACT SURGERY?

All operations and surgical procedures have risks and can have unsuccessful results or associated complications that can injure the patient, or even cause death in some instances. The recognized, specific risks of cataract surgery include problems that can lead to loss of vision, blindness or loss of your eye. Those risks include: bleeding; infection; high eye pressure; a swollen or detached retina; a droopy eyelid; double vision; displacement of the lens or portion (fragments) of the lens; injury to the cornea, iris, sclera, conjunctivae, pupil function, or other parts of the eye and nearby structures, from the operation or the anesthesia. Sometimes pieces of the lens cannot be completely removed and the vitreous can become displaced.

The specific, recognized, risks of a Limbal Relaxing Incision (LRI) or Astigmatic Keratectomy (AK), if performed in conjunction with cataract surgery are similar to those for cataract surgery, but also include perforation to the cornea, damage to the iris, increased astigmatism, and scarring, which could cause loss of vision. Furthermore, the LRI or AK may not fully correct the astigmatism and an under- or over-correction could occur, and glasses, contacts, or another surgical procedure may be needed to correct the vision.
Depending upon your eye and the type of IOL that is used, the most serious, recognized side effects include: increased night glare or halos, double vision, ghost images, impaired depth perception, decreased contrast, blurry vision, and decreased night vision.

At the time of surgery, your ophthalmologist may decide not to implant an IOL even though you may have given prior permission to do so, or your ophthalmologist may decide to implant an IOL different from the one that you initially preferred, or agreed to on pages four and five. In addition, the IOL may later need to be repositioned, replaced, or removed by way of a subsequent surgical procedure.

No intraocular lens or power calculation is perfect and you will likely still need glasses. Calculating IOL power is difficult in patients who are highly nearsighted or farsighted, as well as in patients that have had previous eye surgeries such as cornea surgery, glaucoma surgery, refractive surgery or retina surgery. This difficulty in calculating IOL power may result in your post-operative prescription being different from what you and the doctor thought it would be. This may require you to wear glasses, contact lenses, need refractive surgery, or have an IOL exchange or piggyback lens placed. Furthermore, because only one eye is operated on at a time, you may experience a feeling of imbalance between the two eyes which may require correction.

There is no guarantee that cataract surgery or astigmatism reduction will improve your vision, even with glasses or contacts. You may need glasses or contacts for best vision. In some cases, complications may occur weeks, months or even years later.

OTHER RISKS FROM CATARACT SUGERY:

Depending upon the type of anesthesia that is used, other risks are possible. Local anesthesia may affect or damage the retina, the optic nerve and may lead to: bleeding behind the eye, double vision, and permanent vision loss, perforation of the eye, cardiopulmonary complications, and in rare cases coma or death.

If you have **OTHER KNOWN MEDICAL CONDITIONS**, such as heart disease, history of heart failure, or lung disease such as Asthma or Chronic Obstructive Pulmonary Disease, or if you are **TAKING MEDICATIONS** such as Coumadin (a blood thinner) **OR OTHER SUPPLEMENTS OR VITAMINS**, tell your ophthalmologist so that you can minimize the risk of additional complications during and after surgery.

WHAT ARE MY OUT OF POCKET COSTS?

There is usually an additional charge for multifocal, accommodating, and toric IOLs, which is not paid by insurance. Therefore you understand that you may be responsible for that additional charge.

In some cases, additional sutures to support the IOL or wound, or a vitrectomy (or other additional surgery) may be needed at the time of the procedure or at a later time. The cost for additional surgery is not included in the price paid for the cataract surgery.

I understand that I may need additional treatment with medicines or surgery after my cataract removal. One common occurrence after cataract surgery is a clouding of the capsule behind the IOL requiring a laser treatment months or years later. This additional treatment is not included in the fee for this procedure.

PATIENT'S ACCEPTANCE OF RISKS:

I have read this informed consent (or it has been read to me) and I fully understand it and the possible alternatives to cataract surgery, the risks, complications, and benefits that can result from that surgery.

By signing below, I (we) certify that this form has been fully explained to me (us), that I (we) have filled in all the blank spaces, and that my ophthalmologist has answered all of my (our) questions, and I (we) understand and accept the risks, benefits, and understand the alternatives of cataract surgery.

Patient initials _____
Eye Surgeon's initials _____
Date _____

DOH-MQA 1255, rev. 10/15, Rules 64B8-9.017 and 64B15-14.012

The surgery is on my_____RIGHT EYE _____LEFT EYE

_____I am aware of the recognized specific risks related to cataract surgery that are described in this form.

_____I am aware that no intraocular lens is perfect, and that I may still need to use glasses or contacts for at least some activities or in low light regardless of the type of lens implanted. I am aware that no intraocular lens calculation is perfect, and that it is more difficult in an eye that has had prior corneal surgery or retinal or glaucoma surgery. I am also aware that the intraocular lens may later need to be repositioned, replaced, or removed by way of a subsequent surgical procedure.

On the advice of my Ophthalmologist, he/she and I choose the following premium lenses:

_____Multifocal Intraocular Lens

_____Toric Intraocular Lens (Right eye near/distance; Left eye near/distance).

_____Accommodative Intraocular Lens

_____Monofocal/Monovision lens (Right eye near/distance; Left eye near/distance).

_____Other_____

_____I understand that if during surgery, my ophthalmologist is unable to use any of the premium lenses; I consent to the implantation of a Monofocal Intraocular Lens.

_____I am aware of the recognized specific risks related to Limbal Relaxing Incision (LRI) or Astigmatic Keratectomy (AK) for Astigmatism Reduction are those that are described in this form, and I understand that any of these risks could result in loss of vision, blindness or loss of the eye, and may require me to undergo further surgery. Furthermore, the LRI or AK may not fully correct the astigmatism, and glasses, contacts, or another surgical procedure may be needed to correct the vision.

_____On the basis of the above statements, I voluntarily consent and authorize this cataract surgery procedure.

_____I am aware that I have the right to report adverse incidents to the Florida Board of Medicine or the Florida Board of Osteopathic Medicine.

Patient Print Name: _____

Patient Signature: _____

Date:_____**Time:** _____

(Or person authorized to sign for patient)

Witness Print Name: _____

Witness Signature: _____

Date:_____**Time:** _____

Surgeon Print Name: _____

Surgeon Signature: _____

Date:_____**Time:** _____

Medical Marijuana Consent Form

A qualified physician may not delegate the responsibility of obtaining written informed consent to another person. The qualified patient, or the patient's parent or legal guardian if the patient is a minor, must initial each section of this consent form to indicate that the physician explained the information and, along with the qualified physician, must sign and date the informed consent form.

This consent form contains three parts. Part A must be completed by all patients. Part B is only required for patients under the age of 18 with a diagnosed terminal condition who receive a certification for medical marijuana in a smokable form. Part C is the signature block and must be completed by all patients.

Part A: Must be completed for all medical marijuana patients

a. The Federal Government's classification of marijuana as a Schedule I controlled substance.

_____ The federal government has classified marijuana as a Schedule I controlled substance. Schedule I substances are defined, in part, as having (I) a high potential for abuse; (2) no currently accepted medical use in treatment in the United States; and (3) a lack of accepted safety for use under medical supervision. Federal law prohibits the manufacture, distribution and possession of marijuana even in states, such as Florida, which have modified their state laws to treat marijuana as a medicine.

_____ When in the possession of medical marijuana, the patient or the patient's caregiver must have his or her medical marijuana use registry identification card in his or her possession at all times.

b. The approval and oversight status of marijuana by the Food and Drug Administration.

_____ Marijuana has not been approved by the Food and Drug Administration for marketing as a drug. Therefore, the "manufacture" of marijuana for medical use is not subject to any federal standards, quality control, or other federal oversight. Marijuana may contain unknown quantities of active ingredients, which may vary in potency, impurities, contaminants, and substances in addition to THC, which is the primary psychoactive chemical component of marijuana.

c. The potential for addiction.

_____ Some studies suggest that the use of marijuana by individuals may lead to a tolerance to, dependence on, or addiction to marijuana. I understand that if I require increasingly higher doses to achieve the same benefit or if I think that I may be developing a dependency on marijuana, I should contact Dr._____(name of qualified physician).

d. The potential effect that marijuana may have on a patient's coordination, motor skills, and cognition, including a warning against operating heavy machinery, operating a motor vehicle, or engaging in activities that require a person to be alert or respond quickly.

_____ The use of marijuana can affect coordination, motor skills and cognition, i.e., the ability to think, judge and reason. Driving under the influence of cannabis can double the risk of vehicular accident, which escalates if alcohol is also influencing the driver. While using medical marijuana, I should not drive, operate heavy machinery or engage in any activities that require me to be alert and/or respond quickly and I should not participate in activities that may be dangerous to myself or others. I

understand that if I drive while under the influence of marijuana, I can be arrested for "driving under the influence."

e. The potential side effects of medical marijuana use.

_____ Potential side effects from the use of marijuana include, but are not limited to, the following: dizziness, anxiety, confusion, sedation, low blood pressure, impairment of short term memory, euphoria, difficulty in completing complex tasks, suppression of the body's immune system, may affect the production of sex hormones that lead to adverse effects, inability to concentrate, impaired motor skills, paranoia, psychotic symptoms, general apathy, depression and/or restlessness. Marijuana may exacerbate schizophrenia in persons predisposed to that disorder. In addition, the use of medical marijuana may cause me to talk or eat in excess, alter my perception of time and space and impair my judgment. Many medical authorities claim that use of medical marijuana, especially by persons younger than 25, can result in long-term problems with attention, memory, learning, drug abuse, and schizophrenia.

There is substantial evidence of a statistical association between long-term cannabis smoking and worsening respiratory symptoms and more frequent chronic bronchitis episodes. Smoking marijuana is associated with large airway inflammation, increased airway resistance, and lung hyperinflation. Smoking cannabis, much like smoking tobacco, can introduce levels of volatile chemicals and tar in the lungs that may raise concerns about the risk of cancer and lung disease.

_____ I understand that using marijuana while consuming alcohol is not recommended. Additional side effects may become present when using both alcohol and marijuana.

_____ I agree to contact Dr. _____ if I experience any of the side effects listed above, or if I become depressed or psychotic, have suicidal thoughts, or experience crying spells. I will also contact Dr._____if I experience respiratory problems, changes in my normal sleeping patterns, extreme fatigue, increased irritability, or begin to withdraw from my family and/or friends.

f. **The risks, benefits, and drug interactions of marijuana**.

_____ Signs of withdrawal can include: feelings of depression, sadness, irritability, insomnia, restlessness, agitation, loss of appetite, trouble concentrating, sleep disturbances and unusual tiredness.

_____ Symptoms of marijuana overdose include, but are not limited to, nausea, vomiting, hacking cough, disturbances in heart rhythms, numbness in the hands, feet, arms or legs, anxiety attacks and incapacitation. If I experience these symptoms, I agree to contact Dr. _____ immediately or go to the nearest emergency room.

_____ Numerous drugs are known to interact with marijuana and not all drug interactions are known. Some mixtures of medications can lead to serious and even fatal consequences.

I agree to follow the directions of Dr._____regarding the use of prescription and non-prescription medication. I will advise any other of my treating physician(s) of my use of medical marijuana.

_____ Marijuana may increase the risk of bleeding, low blood pressure, elevated blood sugar, liver enzymes, and other bodily systems when taken with herbs and supplements. I agree to contact Dr. _____ immediately or go to the nearest emergency room if these symptoms occur.

_____ I understand that medical marijuana may have serious risks and may cause low birthweight or other abnormalities in babies. I will advise Dr._____if I become pregnant, try to get pregnant, or will be breastfeeding.

g. The current state of research on the efficacy of marijuana to treat the qualifying conditions set forth in this section.

___ Cancer

- There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma.

  There is evidence to suggest that cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation processes. Due to a lack of recent, high quality reviews, a research gap exists concerning the effectiveness of cannabis or cannabinoids in treating cancer in general.

- There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting.

  There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

___ Epilepsy

- There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy.

  Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence of efficacy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed and await publication.

___ Glaucoma

- There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma.

  Lower intraocular pressure is a key target for glaucoma treatments. Nonrandomized studies in healthy volunteers and glaucoma patients have shown short-term reductions in intraocular pressure with oral, topical eye drops, and intravenous cannabinoids, suggesting the potential for therapeutic benefit. A good-quality systemic review identified a single small trial that found no effect of two cannabinoids, given as an oromucosal spray, on intraocular pressure. The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular

pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma.

___ Positive status for human immunodeficiency virus

- There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

  There does not appear to be good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome.

___ Acquired immune deficiency syndrome

- There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

  There does not appear to be good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome.

___ Post-traumatic stress disorder

- There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder

  A single, small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (plant derived forms) and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder. There are other trials that are in the process of being conducted and if successfully completed, they will add substantially to the knowledge base.

___ Amyotrophic lateral sclerosis

- There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

  Two small studies investigated the effect of dronabinol on symptoms associated with ALS. Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated.

___ Crohn's disease

- There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

  Some studies suggest that marijuana in the form of cannabidiol may be beneficial in the treatment of inflammatory bowel diseases, including Crohn's disease.

___ Parkinson's disease

- There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopainduced dyskinesia.

Evidence suggests that the endocannabinoid system plays a meaningful role in certain neurodegenerative processes; thus, it may be useful to determine the efficacy of cannabinoids in treating the symptoms of neurodegenerative diseases. Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample size limits the interpretation of the data. An observational study demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations.

___ Multiple sclerosis

- There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity.

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS. The effect appears to be modest. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices.

___ Medical conditions of same kind or class as or comparable to the above qualifying medical conditions

- The qualifying physician has provided the patient or the patient's parent or legal guardian a summary of the current research on the efficacy of marijuana to treat the patient's medical condition.
- The summary is attached to this informed consent as Addendum_____.

___ Terminal conditions diagnosed by a physician other than the qualified physician issuing the physician certification

- The qualifying physician has provided the patient or the patient's caregiver a summary of the current research on the efficacy of marijuana to treat the patient's terminal condition.
- The summary is attached to this informed consent as Addendum_____.

___ Chronic nonmalignant pain

- There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

The majority of studies on pain evaluated nabiximols outside the United States. Only a handful of studies have evaluated the use of cannabis in the United
States. and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. Pain patients also use topical forms.

While the use of cannabis for the treatment of pain is supported by well controlled clinical trials, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.

h. That the patient's de-identified health information contained in the physician certification and medical marijuana use registry may be used for research purposes.

_____ The Department of Health submits a data set to the Consortium for Medical Marijuana Clinical Outcomes Research for each patient registered in the medical marijuana use registry that includes the patient's qualifying medical condition and the daily dose amount and forms of marijuana certified for the patient.

PART B: Certification for medical marijuana in a smokable marijuana for a patient under 18 with a diagnosed terminal condition.

____ Initial here if you are not a patient under 18 with a diagnosed terminal condition who will be receiving medical marijuana in a smokable form. After initialing here, complete part C.

If the patient is under 18, has a diagnosed terminal condition, and will be receiving medical marijuana in a smokable form, please review and initial the remainder of Part B before completing Part C.

Respiratory Health

____ Exposures to tobacco smoke and household air pollution consistently ranks among the top risk factors not only for respiratory disease burden but also for the global burden of disease. Given the known relations ships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term cannabis smoking leads to similar deleterious effects of respiratory health, and some investigators ague that cannabis smoking may be even more harmful that of tobacco smoking. Data collected from 15 volunteers suggest that smoking one cannabis joint can lead to four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette.

Cognitive and Psychosocial Development

____ Researchers are still studying the long-term health effects of marijuana. Most people agree that marijuana use hurts adolescents more than adults. It is during the period of adolescence and young adulthood that the neural substrates that underlie the development of cognition are most active. Adolescence marks one of the most impressive stretches of neural and behavioral change with substantial a protracted development in terms of both brain structure and function. As a result, cannabis and other substance use during this period may incur relatively greater interference in neural, social, and academic functioning compared to late developmental periods.

- There is moderate evidence of a statistical association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention.
- There is limited evidence of a statistical association between sustain abstinence form cannabis use and impairments in the cognitive domains of learning, memory, and attention.

- There is limited evidence of a statistical association between cannabis use and impaired academic achievement and education outcomes.
- There is limited evidence of a statistical association between cannabis use and increased rates of unemployment and/or low income.
- There is limited evidence of a statistical association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

____ Addiction

Marijuana, like some other brain-altering substances, can be addictive. Nearly one in 10 marijuana users will become addicted. Starting to use marijuana at a younger age can lead to a greater risk of developing a substance use disorder later in life. Adolescents who begin using marijuana before age 18 are four to seven times more likely than adults to develop a marijuana use disorder.

Part C: For certification of smoking marijuana as an appropriate route of administration for a qualified patient, other than a patient diagnosed with a terminal condition

____ **Acknowledgement of contaminant risks.**

Smokable marijuana has infectious risks that are not present in processed products. Certain molds and mildews can contaminate marijuana plants during growing, processing, storage in dispensaries and in patient homes. These contaminates can pose health risks, particularly to those who are immunosuppressed due to their disease state and treatments. While the State of Florida requires third party testing you should still inspect your product.

____ **Respiratory Health.**

Exposures to tobacco smoke and household air pollution consistently ranks among the top risk factors not only for respiratory disease burden but also for the global burden of disease. Given the known relations ships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term marijuana smoking leads to similar deleterious effects of respiratory health, and some investigators ague that marijuana smoking may be even more harmful that of tobacco smoking.

____ **Information regarding health risks of 2nd and 3rd hand smoke to other household members.**

You should never smoke medical marijuana around other family members, especially children and any household guests. You should smoke outside to allow adequate ventilation and to mitigate the dangers of secondhand and thirdhand smoke to others. Marijuana should never be smoked inside vehicles or other small spaces that children will occupy even if the children are not present at the time the product is consumed.

____ **Dangers of smoking marijuana in households where oxygen is in use.**

If you use oxygen or have others in your household who use oxygen you should not smoke marijuana or any other combustible material in the vicinity of where the oxygen is in use due to the risk of fire and explosion.

____ **Self-dosing, if permitted.**

I have been given instructions or discussed guidance on self- dosing with my qualified physician if permitted to do so.

Part D: Must be completed for all medical marijuana patients

_____ I have had the opportunity to discuss these matters with the physician and to ask questions regarding anything I may not understand or that I believe needed to be clarified. I acknowledge that Dr._____has informed me of the nature of a recommended treatment, including but not limited to, any recommendation regarding medical marijuana.

Dr._____also informed me of the risks, complications, and expected benefits of any recommended treatment, including its likelihood of success and failure. I acknowledge that Dr. _____informed me of any alternatives to the recommended treatment, including the alternative of no treatment, and the risks and benefits. Dr. _____ has explained the information in this consent form about the medical use of marijuana.

Patient (print name) _____

Patient signature or signature of the parent or legal guardian if the patient is a minor:

_____ Date _____

I have explained the information in this consent form about the medical use of marijuana to _____ (Print patient name).

Qualified physician signature:

_____ Date _____

Witness:

_____ Date_____

64B8-9.018, F.A.C.
64815-14.013, F.A.C.
DH-MQA-5026 (Rev. 03/21)

GENder Education and Care Interdisciplinary Support (GENECIS)

Puberty Suppression Treatment for Patients with Gender Dysphoria

Patient Information and Informed Parental Consent and Assent for Minors

Before considering to give treatment to your child to suppress puberty (put puberty "on hold" with "puberty blockers"), you need to be aware of the possible benefits and risks.

After your questions or concerns are addressed and you have decided to proceed with puberty suppression for your child, you will need to initial the statements of this form as well as sign the consent form. If there is more than one parent/legal guardian, both will have to sign. Your child will also need to assent this form.

What are the benefits of suppressing puberty in adolescents with gender dysphoria?

The Endocrine Society recommends suppression of puberty (put puberty "on hold" with "puberty blockers"), for children that have the diagnosis of gender dysphoria as well as other specific criteria listed in the section below. This recommendation was done by experts in treating youth with gender dysphoria, based on the premise that this may: allow for a smooth social transition to the gender role that is congruent with their gender identity; test persistence of the affirmed gender after living a "real-life experience" and before receiving irreversible hormonal or surgical treatment; and diminish the psychological trauma and risk of suicide induced by the physical changes of puberty.

This may also avoid the need for surgery and other expensive treatments that are required to reverse the physical effects of puberty (i.e. mastectomies, tracheal and facial shaving, and electrolysis).

What are my other options if I do not wish to have my child undergo treatment for suppression of puberty?

The only other option available is psychological therapy with a mental health provider that has experience in treating youth with gender dysphoria. We recommend this regardless of whether your child undergoes suppression of puberty or not, due to the high risk of anxiety, depression, self-harm and even suicide. No studies have been done comparing psychological therapy only versus suppression of therapy.

What are the different medications that are used to suppress puberty?

The main mechanism by which physical changes of puberty can be put on hold is by blocking the signal from the brain to the organs that make the hormones of puberty. These hormones are estrogen and testosterone. Estrogen is made by the ovaries. Testosterone is made by the testicles.

The medications are also called "pubertal blockers" and are effective for both males and females. They can be started just after the early physical changes of puberty. None of them have been approved by the Food and Drug Administration (FDA) to be used in adolescents with gender dysphoria, in other words, this is an "off label" use. However, pediatric endocrinologists (children's doctors who specialize in hormones and puberty), use these medications frequently to suppress puberty in children with precocious (early) puberty.

Lupron and Histrelin are called GnRH analogs and are the most effective forms of treatment. Lupron is given as a monthly or every 3 month intramuscular injection and is approved for children with precocious (early) puberty. Histrelin is an implant that is placed under the skin surgically, and needs to be replaced yearly to every 2 years. Histrelin is approved for children with precocious puberty with the brand name of Supprelin, and on a slightly smaller dose, it is approved in adults with prostate cancer under the name of Vantas. Provera is a pill that needs to be taken twice a day and is approved to be used in female adolescents with abnormal uterine bleeding. Provera was used for early puberty before Lupron and Histrelin were available, and is less effective in suppressing puberty.

What are the requirements to receive suppression of puberty for gender dysphoria in our program?

In order to receive therapy to put puberty on "hold" at our center, there are specific requirements that need to be met before and during the treatment. Although this therapy is considered standard of care, this is a new area of medicine and we want to provide the safest treatment. These requirements will allow us to monitor your child's medical as well as mental health wellbeing during hormone therapy. If these requirements are not met, treatment with puberty blockers may be discontinued in the best interest and safety of your child.

Before beginning treatment with a "puberty blocker" your child needs to undergo a thorough psychological and social evaluation performed by our GENECIS team. We also require your child has participated in at least 6 months of psychological therapy. We will need a letter from your child's therapist confirming this. Your child will need to have started puberty, which varies from person to person but usually occurs after age 8.

After all this has taken place, treatment to suppress puberty can be initiated if your child meets specific criteria established by the Endocrine Society, which includes ALL of the following:

1. Fulfill the current DSM or ICD criteria for gender dysphoria or transsexualism.
2. Have (early) pubertal changes that have resulted in an increase in gender dysphoria.
3. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
4. Have adequate psychological and social support during treatment.
5. Have experienced puberty to at least Tanner stage 2 : this is the first stage of puberty and refers to breast or testicle growth; has to be confirmed by a physician.
6. Demonstrate knowledge and understanding of the expected outcomes of suppression of puberty, future cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and social risks and benefits of sex reassignment.

After treatment for suppression of puberty has been initiated, the following will be required:

1. Visits with the endocrinologist or adolescent medicine physician in our program every 3 months.

2. Suicide risk assessment performed by our social worker during each clinic visit every 3 months.

2. Laboratory testing every 3-4 months.

3. Xray of the hand (bone age) once a year.

4. Bone (dexa) scan: this will allow us to monitor your child's bone density (bone strength) during treatment, since puberty blockers may decrease bone density if given for long periods of time.

5. Yearly mental health assessment and completion of questionnaires with a member of our mental health care team. This will allow us to monitor your child's psychological wellbeing and adjustment while on puberty blockers.

6. Continued counseling with a therapist during the treatment period, with the frequency recommended by the therapist.

Please initial each statement on this form to show that you understand the benefits, risks, and changes that may occur from giving treatment for suppression of puberty to your child.

Effects of Treatment of Suppression of Puberty

_____ I know that puberty blockers are used to help temporarily suspend or block the physical changes of puberty for my child.

_____ I know that the effect of this medication is not permanent. If my child stops treatment, in a few months my child's body will restart the changes of puberty at the developmental stage they were at when they started the treatment.

_____ I know that it can take several months for the medication to be effective. I know that no one can predict how quickly or slowly my child's body will respond.

_____ I know that by taking these medications, my child's body will not be making the hormones of puberty, testosterone or estrogen. At this time, I support my child in "putting on hold" the hormones and the changes induced by puberty.

_____ I know that the use of these medications in adolescents with gender dysphoria are off-label use. I know this means it they are not approved by the FDA for this specific diagnosis.

Risks of Treatment of Suppression of Puberty

_____ I know that information on adverse effects and safety of these medications used in transgender youth is not well known.

_____ I realize that this treatment may not be able to completely prevent serious psychiatric events such as a suicidal attempt.

_____ I know that the treatments to suppress puberty may induce weight gain.

_____ I know that the treatments to suppress puberty may decrease bone density.

_____ I know that my child may grow less than his/her peers while on these medications.

I realize there may be a stalling of typical adolescent cognitive or brain development while on these medications.

I know that stopping the development of puberty for my child may have social consequences.

Requirements of Treatment of Suppression of Puberty

I understand and agree with all the requirements explained above, in order to receive suppression of puberty therapy in our program.

_____ I know that the mental health team and/or treating physician may recommend to stop treatment because it no longer outweighs the risks, there is insufficient social or psychological support, or our program requirements to treat are not met. In this case, we will not continue to prescribe drug therapy.

_____ I know that I am responsible for the cost of the medical management, including medical appointments, psychological evaluations, laboratory and imaging tests, as well as drug therapy.

_____ I know that I can change my mind and decide to stop treatment at any time.

_____ I agree to tell a member of our GENECIS team if you think your adolescent has any problems or is unhappy with the treatment.

_____ I know that after my child turns 21, medical care will have to be transitioned to an adult endocrinologist.

Prevention of Complications while under Treatment of Suppression of Puberty

_____ I agree to tell my health care provider if my child has any problems or side effects or is unhappy with the medication, and in particular, if you have concerns that your child has worsening signs of depression or anxiety, or wants to harm him/herself or attempt suicide.

_____ I know my child needs periodic medical evaluations clinic to make sure that my child is responding appropriately. This includes clinic visits with the pediatric endocrinologist or adolescent medicine every 3 months, laboratory and imaging tests.

_____ I agree to have my child on continued psychological therapy or counseling with the frequency recommended by his therapist.

PARENTAL CONSENT:

Our signatures below confirm that

- My child's health care provider has talked with me about:
  a) the benefits and risks of puberty blockers for my child.
  b) the possible or likely consequences of using puberty blockers.
  c) potential alternative treatments.
- I understand the risks that may be involved.

- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects or risks.
- I agree with the requirements to receive puberty blockers in this program.
- I have had enough opportunity to discuss treatment options with my child's health care provider.
- All of my questions have been answered to my satisfaction.
- I believe I know enough to give informed consent for my child to take, refuse, or postpone using puberty blocking medications.
- My child is in agreement with this treatment and the signature of my child on the assent form attests to this agreement.
- My signature attests to my consent for my child to begin treatment for suppression of puberty.

Based on all this information:

_____ I want my child to receive puberty suppression treatment as prescribed.

_____ I do not wish my child to receive puberty suppression treatment at this time.

_____
Parent or legal guardian's name

_____ _____
Parent or legal guardian's signature Date

_____
Parent or legal guardian's name

_____ _____
Parent or legal guardian's signature Date

_____
Prescribing clinician's name

_____ _____
Prescribing clinician's signature Date

ASSENT OF A MINOR:

I have discussed the benefits and risks of treatment to suppress puberty with my parent(s) or legal guardian(s), and I wish to receive it.

Minor's Name (printed)

Minor's Signature Date

GENder Education and Care Interdisciplinary Support (GENECIS)

Feminizing Medications for Patients with Gender Dysphoria

Patient Information and Informed Consent and Assent for Minors

Before using medications to transition your adolescent to her/his affirmed gender, you need to be aware of the possible advantages, disadvantages and risks of these medications. We have listed them here for you.

Once your questions or concerns are addressed, and you have decided to proceed with the medication(s), you will need to sign this information and consent form. If there is more than one parent/legal guardian, both will have to sign. Your child will also need to assent this form.

What are the different medications that can feminize one's appearance?

Part of transition for many transgender people involves taking hormones, this is also called hormone replacement therapy or HRT. HRT in transgender girls and women means taking estrogens (female hormones), as well as medicines to block their body from producing or utilizing testosterone (male hormones). Use of these medications in adolescents with gender dysphoria, is considered "standard of care" as long as they also meet specific criteria listed below, but these medications do not have the FDA indication to be used in this population, in other words, it is "off label use".

Different forms of the hormone estrogen are used to feminize appearance in transgender females. Estrogen can be given as an injection to be given weekly or every other week, as a pill to be taken daily or twice a day, or as a patch to be changed every three or four days.

Medications that block the production or effects of testosterone are called androgen blockers. Androgen is another term for male sex hormones. Spironolactone is the androgen blocker that is most commonly used in the United States. Other medicines are sometimes used, but because spironolactone is relatively safe, inexpensive, and effective to block testosterone, it is the primary androgen blocker used for transgender women.

Every medication has risks, benefits, and side effects that are important to understand before starting. The effects and side effects of medicines used for transition need to be monitored with laboratory studies and regular visits to your child's provider, to make sure that there are no negative medical and mental health effects.

Both these medicines, as well as the process of transitioning can affect your adolescents' mood. While trans women are usually relieved and happy with the changes that occur, it is important that your child is under the care of a gender-qualified therapist while undergoing transition. The therapist can work with your child, your family and friends and your school staff.

Alternatives

There are alternatives to using feminizing medicines to help people appear more feminine. Some transgender people choose to not take hormones or have surgery and may only socially transition. If you are interested in alternatives, talk with your adolescent's health care provider about options.

What are the requirements to receive hormone replacement therapy (HRT) in our program?

In order to receive hormone replacement therapy (HRT) in our program, there are specific requirements that need to be met before and during the treatment. Although this therapy is considered standard of care, this is a new area of medicine for adolescents, and we want to provide the safest treatment possible. These requirements will allow us to monitor your child's medical as well as mental health wellbeing during HRT. If these requirements are not met, HRT may be discontinued in the best interest and safety of your child.

Before beginning HRT your child needs to undergo a thorough psychological and social evaluation performed by our GENECIS team. We also require your child has participated in at least 6 months of psychological therapy. We will need a letter from your child's therapist confirming this.

After all this has taken place, HRT can be initiated if your child meets the criteria established by the Endocrine Society, which includes ALL of the following:

1. Fulfill the current DSM or ICD criteria for gender dysphoria or transsexualism.
2. Have pubertal changes that have resulted in an increase in gender dysphoria.
3. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
4. Have adequate psychological and social support during treatment.
5. Have experienced puberty to at least Tanner stage 2 (first stage of puberty)
6. Demonstrate knowledge and understanding of the expected outcomes of HRT and sex reassignment surgery, as well as the medical and social risks and benefits of sex reassignment.

AND EITHER:

7. Your child is ≥16 years old and has experienced a full social transition to the desired gender for ≥1 year.

OR

8. Your child is 14-15 years of age, has experienced a full social transition to the desired gender for ≥2 years and has been on a puberty blocker for ≥ 1 year.

After HRT has been initiated, the following will be required:

1. Visits with the endocrinologist or adolescent medicine physician in our program every 3 months.

2. Suicide risk assessment performed by our social worker during each clinic visit every 3 months.

2. Laboratory testing every 3-6 months.

3. X ray of the hand (bone age) once a year if your child is still growing.

4. Bone (dexa) scan once a year: this will allow us to monitor your child's bone density (bone strength) during treatment, which can be altered by HRT.

5. Yearly mental health assessments and completion of questionnaires with a member of our mental health care team. This will allow us to monitor your child's psychological wellbeing and adjustment while on HRT.

6. Continued counseling with a therapist during the treatment period, with the frequency recommended by the therapist.

What are the effects and risks of using these medications?

Estrogen can cause blood clots. We must be careful that your child is not at risk to develop a blood clot. Who should not take estrogen?

Estrogen should not be used by anyone who has a history of

- An estrogen-dependent cancer
- A disorder that makes them more likely to get blood clots that could travel to the lungs (unless they are also taking blood thinners and are followed by a specialist)

Estrogen should be used with caution and only after a full discussion of risks by anyone who

- Has a strong family history of breast cancer or other cancers that grow quicker when estrogens are present
- Has uncontrolled diabetes
- Has heart disease
- Has chronic hepatitis or other liver disease
- Has uncontrolled high cholesterol
- Has migraines or seizures
- Is obese
- Smokes cigarettes

Please initial each statement on this form to show that you understand the benefits, risks, and changes that may occur from taking these medications.

Effects of Feminizing Medications

_____I know that estrogen, anti-androgens, or both may be prescribed to feminize your adolescent's appearance.

_____ _____ I know it can take several months or longer for the effects to become noticeable. I know that no one can predict how fast – or how much – change will happen.

I know that taking estrogen will cause the following changes to your adolescent's breasts:

- Will develop breasts.
- It takes several years for breasts to get to their full size.
- The breasts will remain, even if estrogen is stopped.
- A milky discharge from the nipples may appear. If this happens, this should be checked with your child's provider. It could be caused by the estrogen or by something else.

- While we do not know the exact risk, the risk of breast cancer may be increased to as high as if your child had been born female.

_____ I know that the following changes are usually not permanent — they are likely to go away if the medicines are stopped:

- If body hair is present, it will become less noticeable and will grow more slowly although it won't stop completely, even after taking medicines for years.
- There might be less fat on the abdomen and more on the buttocks, hips, and thighs. The fat will be redistributed to a more female shape — changing from —apple shape to —pear shape.
- Your child may lose muscle and strength in the upper body.
- The skin may become softer.

_____ _____ I know that your adolescent's body will make less testosterone. This may affect sex life in different ways and the future ability to cause a pregnancy:

- The testicles may shrink down to half their size.
- It is likely that there will be fewer spontaneous erections.
- Sperm may no longer get to mature. This could makes your adolescent less likely to cause a pregnancy while taking hormones and may be a permanent change even hormone therapy is discontinued.
- There is a risk your child will never produce mature sperm again and this risk is further increased if your child took puberty suppressing hormones ("puberty blockers"), prior to starting feminizing medications.
- However, it is also possible that the sperm could still mature even while taking hormones. So, I know that my adolescent may get someone pregnant.
- The options for sperm banking have been explained.

_____ _____ I know that some parts of the body will not change much by using these medicines.

- If present, the hair of the beard and moustache may grow more slowly than before. It may become less noticeable, but it will not go away.
- If your child went through a "male puberty" and have a "male voice", the pitch of the voice will not rise, and the speech patterns will not become more like a woman's.
- If present, the "Adam's apple" will not shrink.
- Although these medicines can't make these changes happen, there are other treatments that may be helpful.

___ ___ I know that there may be mood changes with these medicines. I agree to hie my alolescent conti nue therapy with aqualif ied therapist.

___ ___ I know that using these medicines to feminize is an off-lel use. This means it is not approved by the Food and Drug Administration (FDA). I know that the medicine and dose that is recommended is based on the judgment and experience of your child's health care provider and the best information that is currently iaille in the medical literature.

Risks of Feminizing Medications

___ ___ I know that the side effects and safety of these medicines are not completely known. There may be long-term risks that are not yet known.

_____ I realize that this treatment may not be leto completely prient serious psychiatric ients such as a suicidal attempt.

___ ___ I know that my child should not tce more medicine than prescribed. Tcing too much medication:

- Will increasehealth risks
- Won't make changes happen more quickly or more significantly

_____ _____ I know these medicines may damage the liver and may leJ to liver disease. Therefore, I should be checked for possible liver damage as long as I take them.

___ ___ I know these medicines cause changes that other people will notice. Some transgender people hie experienced discrimination because ofthis. I know my child's clinician can help me find a1vocay and support resources.

Risks of Estrogen

___ ___ I know that tcing estrogen increases the risk of blood clots or problems with blood vessels which are rare in young people but that can result in:

- Chronic problems with veins in the legs
- Heart attk
- Pulmonary embolism - blood clot to the lungs- which may cause permanent lung damage or death
- Stroke, which may cause permanent brain damage or death

____ ____ I know that the risk of blood clots is much worse if your child smokes cigarettes. The danger isso high that your child should stop smoking completely if estrogen is started.

____ ____ I know tci ng estrogen can increase the deposits of fat around internal organs. This can increase the risk for diabetes and heart disease.

____ ____ I know tci ng estrogen can raise blood pressure.

____ ____ I know that tcing estrogen increasesthe risk of getting gallstones, and I should talk our child's clinician if severe or long-lasting pain in the abdomen occurs

_____ _____ I know that estrogen can cause nausea and vomiting, and I should talk with our child's clinician if long-lasting nausea or vomiting occurs.

____ ____ I know that estrogen can cause migraines or mace them worse if your child alreJy has them.

____ ____ I know that it is not yet known if taking estrogen increases the risk of prol ti nomas. These are non-cancerous tumors of the pituitary gland. I know they are not usually life threatening, but they can damage vision and cause heJahes if th' are not treated properly. Therefore, if your child has changes in vision, heJhesthat areworsewhen wcing up in the morning, and milky dischargefrom the nipples, these can be signs of a prolti noma, and I should talk to my child's provider. There is a blood test that can check for this.

Risks of Androgen Antagonists

____ ____ I know that spi ronol atone affects the balance of water and salts in the kidneys This may:

- Increase the amount of urine produced, mcing it necessary to urinate more frequently.
- Increasethirst.
- Increase risk of dehydration (not hiing enough water), and your child should mcesure to drink plenty of water in hot weather.
- Rarely, cause high levelsof potassium inthe blood, which can causechanges in heart rhythms that may be life threatening. Your child's doctor will perform a blood test to monitor this risk while on the medication.
- Reduce blood pressure.

Requirements for HIRT at the GENECIS program:

in our program.

_____ I know that the mental health team and/or treating physician may recommend to stop treatment because it no longer outweighs the risks, there is insufficient social or psychological support, or our program requirements to treat are not met. In this case, we will not continue to prescribe drug therapy.

_____ I know that I am responsible for the cost of the medical management, including medical appointments, psychological evaluations, laboratory and imaging tests, as well as drug therapy.

_____ I know that I can change my mind and decide to stop treatment at any time.

_____ I know that after my child turns 21, medical care will have to be transitioned to an adult endocrinologist.

Prevention of Complications while under Treatment of HRT

_____ I agree to tell my health care provider if my child has any problems or side effects or is unhappy with the medication, and in particular, if you have concerns that your child has worsening signs of depression or anxiety, or wants to harm him/herself or attempt suicide.

_____ I know my child needs periodic medical evaluations clinic to make sure that my child is responding appropriately. This includes clinic visits with the pediatric endocrinologist or adolescent medicine every 3 months, laboratory and imaging tests.

_____ I agree to have my child on continued psychological therapy or counseling with the frequency recommended by his therapist.

Our signatures below confirm that:

- My clinician has talked with me and my child about:
  - The benefits and risks of taking feminizing medication
  - The possible or likely consequences of hormone therapy
  - Potential alternative treatments
- I understand the risks that may be involved.
- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects of risks.
- I have had enough opportunity to discuss treatment options with our child's clinician.

- My child is in agreement with this treatment and the signature of my child on the assent form attests to this agreement.
- All of my questions have been answered to my satisfaction.
- I believe I know enough to give informed consent to take, refuse, or postpone therapy for my adolescent child with feminizing medications.

Based on all this information:

_____ _____ I want my adolescent child to begin taking estrogen.

_____ _____ I want my adolescent child to begin taking androgen antagonists (e.g., spironolactone).

_____ _____ I do not wish my adolescent child to begin taking feminizing medication at this time.

_____
Parent or legal guardian's name

_____ _____
Parent or legal guardian's signature Date

_____
Parent or legal guardian's name

_____ _____
Parent or legal guardian's signature Date

_____
Prescribing clinician's name

_____ _____
Prescribing clinician's signature Date

ASSENT OF A MINOR:

I have discussed the benefits and risks of treatment with feminizing medication with my parent(s) or legal guardian(s), and I wish to receive it.

Minor's Name (printed)

Minor's Signature Date

Testosterone Treatment for Patients with Gender Dysphoria

Patient Information and Informed Consent and Assent for Minors

Before using testosterone to transition and masculinize your adolescent's body, you need to be aware the possible advantages, disadvantages and risks. We have listed them here for you. It's important that you understand all of this information before you agree to having your adolescent begin taking testosterone.

Once your questions or concerns are addressed, and you have decided to proceed with the testosterone treatment, you will need to sign this information and consent form. If there is more than one parent/legal guardian, both will have to sign. Your child will also need to assent this form.

What is testosterone and why is it used in people with gender dysphoria?

Part of transition for many transgender people involves taking hormones, this is also called hormone replacement therapy or HRT. HRT in transgender males means taking testosterone. This is the sex hormone that makes certain features appear typically male. It builds muscle and causes the development of facial hair and a deeper voice.

Use of these testosterone in adolescents with gender dysphoria, is considered "standard of care" as long as they also meet specific criteria listed below, but these medications do not have the FDA indication to be used in this population, in other words, it is "off label use".

Alternatives

There are alternatives to using HRT to help people appear more male. Some transgender people choose to not take hormones or have surgery and may only socially transition. If you are interested in alternatives, talk with your adolescent's health care provider about options.

How is testosterone taken?

It is usually injected every one to four weeks. It is not used as a pill because the body may not absorb it properly and may cause potentially fatal liver problems. Some people use skin creams and patches, but they tend to be more expensive and aren't recommended for initiating puberty or for use in teenagers and young adults.

The doses used for injection differ from product to product and from patient to patient. They may range from 50 to 400mg. The injections are given in the muscle (intramuscular). It can also be given with a smaller needle under the skin (subcutaneous), this method is also effective in practice although it is considered "off label". Your child may experience unwanted swings in hormone levels. They swings might be affected by how often the dose is given and how much of a dose is given.

Every medication has risks, benefits, and side effects that are important to understand before starting. The effects and side effects of medicines used for transition need to be monitored with laboratory studies and regular visits to your child's provider to make sure that there are no negative medical or mental health effects.

Both testosterone, as well as the process of transitioning can affect your child's mood. While trans men are usually relieved and happy with the changes that occur, it is important you're your child is under the care of a gender-qualified therapist while undergoing transition. The therapist can work with your child, your family and friends and your school staff.

What are the requirements to receive hormone replacement therapy (HRT) in our program?

In order to receive hormone replacement therapy (HRT) in our program, there are specific requirements that need to be met before and during the treatment. Although this therapy is considered standard of care, this is a new area of medicine for adolescents, and we want to provide the safest treatment possible. These requirements will allow us to monitor your child's medical as well as mental health wellbeing during HRT. If these requirements are not met, HRT may be discontinued in the best interest and safety of your child.

Before beginning HRT your child needs to undergo a thorough psychological and social evaluation performed by our GENECIS team. We also require your child has participated in at least 6 months of psychological therapy. We will need a letter from your child's therapist confirming this.

After all this has taken place, HRT can be initiated if your child meets the criteria established by the Endocrine Society, which includes ALL of the following:

1. Fulfill the current DSM or ICD criteria for gender dysphoria or transsexualism.
2. Have pubertal changes that have resulted in an increase in gender dysphoria.
3. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
4. Have adequate psychological and social support during treatment.
5. Have experienced puberty to at least Tanner stage 2 (first stage of puberty)

6. Demonstrate knowledge and understanding of the expected outcomes of HRT and sex reassignment surgery, as well as the medical and social risks and benefits of sex reassignment.

AND EITHER:

7. Your child is ≥16 years old and has experienced a full social transition to the desired gender for ≥1 year.

OR

8. Your child is 14-15 years of age, has experienced a full social transition to the desired gender for ≥2 years and has been on a puberty blocker for ≥ 1 year.

9. After HRT has been initiated, the following will be

required:

1. Visits with the endocrinologist in our program every 3 months.

2. Suicide risk assessment performed by our social worker during each clinic visit every 3 months.

2. Laboratory testing every 3-6 months.

3. X ray of the hand (bone age) once a year if your child is still growing.

4. Bone (dexa) scan once a year: this will allow us to monitor your child's bone density (bone strength) during treatment, which can be altered by HRT.

5. Mental health assessments and completion of questionnaires with a member of our mental health care team every 3 months. This will allow us to monitor your child's psychological wellbeing and adjustment while on HRT.

6. Continued counseling with a therapist during the treatment period, with the frequency recommended by the therapist.

Effects of testosterone

Warning Who should not take testosterone?

It should *not* be used by anyone who is pregnant or has uncontrolled coronary artery disease as it could increase your risk for a fatal heart attack:

It should be used with caution and only after a full discussion of risks by anyone who

- Has acne
- Has a family history of heart disease or breast cancer
- Has had a blood clot
- Has high levels of cholesterol
- Has liver disease
- Has a high red-blood-cell count
- Is obese
- Smokes cigarettes

Periodic blood tests to check on the effects of the hormone will be needed. Routine breast exams and pelvic exams with Pap tests should be continued, when applicable.

Summary of Testosterone Benefits and Risks

BENEFITS	RISKS
• Appearing more like a man o Bigger clitoris o Coarser skin o Lower voice o More body hair o More facial hair o More muscle mass o More strength o No more menstrual periods • More physical energy • More sex drive • Protection against bone thinning (osteoporosis)	• Acne (may permanently scar) • Blood clots (thrombophlebitis), risk significantly increased by smoking • Emotional changes, for example, more aggression • Headache • High blood pressure (hypertension) • Increased red-blood-cell count • Infertility • Inflamed liver • Interaction with drugs for diabetes and blood thinning – for example Coumadin and Warfarin • Male pattern baldness

	• More abdominal fat — redistributed to a male shape • More risk of heart disease • Swelling of hands, feet, and legs • Weight gain

Please initial each statement on this form to show that you understand the benefits, risks, and changes that may occur from taking testosterone.

Masculinizing Effects

_____ _____ I know that testosterone may be prescribed to make your adolescent appear less like a female and more like a male.

_____ _____ I know it can take several months or longer for the effects to become noticeable. I know that no one can predict how fast – or how much – change will happen. I know that the changes may not be complete for two to five years after started.

_____ _____ I know that the following changes are likely and permanent even if testosterone is discontinued:

- Bigger clitoris — typically about half an inch to a little more than an inch
- Deeper voice
- Gradual growth of moustache and beard
- Hair loss at the temples and crown of the head — possibility of being completely bald
- More, thicker, and coarser hairs on abdomen, arms, back, chest, and legs

_____ _____ I know that the following changes are usually not permanent — they are likely to go away if I stop taking testosterone:

- Acne (although there may be permanent scars)
- Menstrual periods (if present), typically stop one to six months after starting
- More abdominal fat – redistributed to a male shape: decreased on buttocks, hips, and thighs; increased in abdomen – changing from "pear shape" to "apple shape"
- More muscle mass and strength
- More sexual interest
- Vaginal dryness

____ ____ *I know that the effects of testosterone on fertility are unknown. I hie been told* that your child may or may not be leto get pregnant even if testosterone is discontinued. I know that your child may still get pregnant even after testosteronestops menstrual periods

_____ _____ I know that some aspects of the body will not be changed:

- Losing some fat may me breasts appear slightly smaller (if present), but th' will not shrink very much.
- The voice will deepen, but other aspects of the way your alolescent spes may not sound more masculine.
- Although testosterone can't make these changes happen, there are other treatments that may be helpful.

____ ____ *I know that there may be mood changes with these medicines. I agree to hie my* child continuetherapy with aquified therapist.

_____ I know that using testosterone is an off-lel use in this population. This means it is not approved by the Food and Drug Administration (FDA). I know that the medicine and dose that is recommended is based on the judgment and experience of your child's health care provider and the best information that is currently availlle in the medical literature.

Risks of Testosterone

____ ____ *I know the medical effects and the safety of testosterone are not completely* known. There may be long-term risks that are not yet known.

_____I realize that thistreatment may not beleto completely prevent serious psychiatric events such as a suicidal attempt.

____ ____ *I know that your child should not te more testosteronethan prescribed. Tdng* too much:

- Will increase health risks
- Won't make changes happen more quickly or more significantly
- Can cause the body to convert extra testosterone into estrogen, and that can slow down or stop my appearing more masculine

____ ____ I know that testosterone can cause changes that increase the risk of heart disease in Julthood. These changes include hiing:

- Less good cholesterol (HDL) that may protect against heart disease and more bal cholesterol (LDL) that may increase the risk of heart disease
- Higher blood pressure
- More deposits of fat around the internal organs

____ ____ I know testosterone can damage the liver and possibly leal to liver disease and your child should bechecked for possible liver damagewhiletdng testosterone.

____ ____ I know testosteronecan increase red blood cells and hemoglobin. This increase is usually only to what is normal for a man and shouldn't cause any health risks. However, there is a small possi bility that higher lielsof red blood cells and hemoglobin may increase my risk of life-threatening problems such as stroke or heart attack. That's why I know your child will need periodic blood checks while testosterone.

___ ___ I know that td ng testosterone can increase the risk for dietes. It may decrease the body's response to insulin, cause weight gain, and increase deposits of fat around internal organs Therefore, your child should hie periodic checks of my blood glucose while td ng testosterone.

____ ____ I know that testosterone can give heJhes or migraines. I know that it's best to talk with your child's clinician if migraines occur often or if the pain is unusually severe.

____ ____ I know that testosterone can cause emotional changes. For example, your child could become more irritable, frustrated, more aggressive or angry.

___ ___ I know that testosterone causes changes that other people will notice. Some transgender people hie experienced harassment, discrimination, and violence because of this.

Requirements for HIRT at the GENECIS program:

____ I understand and agree with all the requirements explained ove, in order to receive HRT in our program.

_____ I know that the mental heath team and/or treating physician may recommend to stop treatment because it no longer outweighs the risks, there is insufficient social or psychological

support, or our program requirements to treat are not met. In this case, we will not continue to prescribe drug therapy.

_____ I know that I am responsible for the cost of the medical management, including medical appointments, psychological evaluations, laboratory and imaging tests, as well as drug therapy.

_____ I know that I can change my mind and decide to stop treatment at any time.

_____ I know that after my child turns 21, medical care will have to be transitioned to an adult endocrinologist.

Prevention of Complications while under Treatment of HRT

_____ I agree to tell my health care provider if my child has any problems or side effects or is unhappy with the medication, and in particular, if you have concerns that your child has worsening signs of depression or anxiety, or wants to harm him/herself or attempt suicide.

_____ I know my child needs periodic medical evaluations clinic to make sure that my child is responding appropriately. This includes clinic visits with the pediatric endocrinologist or adolescent medicine every 3 months, laboratory and imaging tests.

_____ I agree to have my child on continued psychological therapy or counseling with the frequency recommended by his therapist.

PARENTAL CONSENT:

Our signatures below confirm that:

- My clinician has talked with me about:
  - The benefits and risks of taking testosterone
  - The possible or likely consequences of hormone therapy
  - Potential alternative treatments
- I understand the risks that may be involved.
- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects of risks.
- I have had enough opportunity to discuss treatment options with our child's clinician.
- My child is in agreement with this treatment and the signature of my child on the assent form attests to this agreement.
- All of my questions have been answered to my satisfaction.
- I believe I know enough to give informed consent to take, refuse, or postpone testosterone therapy for my child.

Based on all this information:

_____ _____ I want my adolescent to begin taking testosterone.

_____ _____ I do not wish my adolescent to begin taking testosterone at this time.

Parent or legal guardian's name

Parent or legal guardian's signature Date

Parent or legal guardian's name

_____ _____
Parent or legal guardian's signature Date

_____
Prescribing clinician's name

Prescribing clinician's signature Date

ASSENT OF A MINOR:

I have discussed the benefits and risks of treatment testosterone with my parent(s) or legal guardian(s), and I wish to receive it.

Minor's Name (printed)

Minor's Signature Date

INFORMED CONSENT FORM
ESTROGEN THERAPY FOR GENDER DYSPHORIA

The cause of gender dysphoria is not known, but is thought to be partly due to genetic or environmental causes affecting the early development of my brain pathways. I understand that the effect of this on me means that, even though I think of myself partially or completely as female, I am genetically, biologically and physically male. I want to receive treatment that will help me change my body towards that of a female, so that it will match my sense of myself (my gender identity).

With the understanding and consent of my parents/guardians, I may have been taking a medicine called Lupron Depot@ to stop me from going through puberty as a male. I may also have been taking an anti-androgen medication called spironolactone to prevent beard growth. Regardless, my treatment also involves "talking therapy" (psychotherapy) to help me think about all the possible results and consequences of going part or all the way through the physical change, called "transition", from a male towards a female body.

I understand that I may now begin taking the female hormone estrogen, up to a dose that would be normal for females my age. I understand that estrogen will cause my body to become more feminine in appearance, and it will reduce my male hormones. I know that this treatment will not change my genetic sex (chromosomes), and it will not change my external genitals (penis and testicles).

I understand that, although estrogen is a common treatment for adults with gender dysphoria, using this treatment in young adolescents is a newer development, and the long-term effects are not fully known. It has been explained to me that doctors are prescribing estrogen because they believe that I will continue towards full or partial physical transition to a female body, perhaps including eventual surgery to remove or reshape my external male genitals. However, taking estrogen now does not guarantee that I will eventually want, need, or have this surgery. Gender-affirming surgery has to be talked about in detail when I am further along in my transition, and final decisions can only be made after I have been living in the gender role that is congruent with my gender identity for a period of time.

There are also possible long-term considerations and risks of estrogen use in natal males, as follows:

1. The feminizing effects of estrogen can take several months or longer to become noticeable, and that the rate and degree of change can't be completely predicted, and changes may not be complete for 2-5 years after starting estrogen.

2. Taking estrogen will cause breast development:
   - Breasts may take several years to develop to their full size.
   - Even if estrogen is stopped, the breast tissue that has developed will remain.
   - As soon as breasts start growing, it is recommended to start doing monthly breast self-examinations and to have an annual breast exam by a doctor or nurse.
   - There may be milky nipple discharge (galactorrhea). This can be caused by taking estrogen or by an underlying medical condition. It is advised to check with a doctor to determine the cause.
   - It is thought that taking estrogen can increase the risk of breast cancer to that of non-trans women.

3. The following changes are generally not permanent (that is, they will likely reverse if estrogen is discontinued):
   - Skin may become softer.
   - Muscle mass decreases and there may be a decrease in upper body strength.

- Body hair growth may become less noticeable and grow more slowly, but it not necessarily stop completely, even after years on medication.
- Male-pattern baldness may slow down, but will probably not stop completely, and hair that has already been lost will likely not grow back.
- Fat may redistribute to a more feminine pattern (decreased in abdomen, increased on buttocks/hips/thighs—changing from "apple shape" to "pear shape").

4. Taking estrogen will make the testicles produce less testosterone, which can affect overall sexual function:
   - Sperm may not mature, leading to reduced fertility. The ability to make sperm normally may or may not come back even after stopping taking estrogen. The options for sperm banking will be reviewed.
   - You will still be able to make someone pregnant, and you need to be aware of birth control options (if applicable). You still need to protect yourself from sexually transmitted infections.
   - Testicles may shrink by 25-50%. Regular testicular examinations are still recommended.
   - The amount of fluid ejaculated may be reduced.
   - There is typically a decrease in morning and spontaneous erections.
   - Erections may not be firm enough for penetrative sex.
   - Libido (sex drive) may decrease.
5. There are some aspects of the body that are not significantly changed by taking estrogen:
   - Beard/moustache hair may grow more slowly and be less noticeable, but it will not necessarily go away.
   - Voice pitch will not rise, and speech patterns will not become more feminine.
   - The Adam's apple will not shrink.
6. Taking estrogen can theoretically damage the liver, possibly leading to liver disease. You should be monitored for possible liver damage as long as you are taking estrogen.
7. Taking estrogen increases the risk of blood clots, which can result in:
   - pulmonary embolism (blood clot to the lungs), which may cause permanent lung damage or death
   - stroke (blood clot in the brain), which may cause permanent brain damage or death
   - heart attack
   - chronic leg vein problems
8. The risk of blood clots is much higher when a person smokes cigarettes. The danger is so high that you are advised to stop smoking completely if you start taking estrogen. The doctor can provide you with advice about options to stop smoking.
9. Taking estrogen can increase deposits of fat around the internal organs, which is associated with increased risk for diabetes and heart disease.
10. Taking estrogen can cause increased blood pressure. If you develop high blood pressure, the doctor will work with you to try to control it by diet, lifestyle changes, and/or medication.
11. Taking estrogen increases the risk of gallstones. If you have abdominal pain that is severe or prolonged, it is recommended that you discuss this with your doctor.
12. Taking estrogen can cause nausea and vomiting, similar to morning sickness in pregnant women. If nausea/vomiting are severe or prolonged, it is recommended that you discuss this with your doctor.
13. Taking estrogen can cause headaches or migraines. If you are frequently having headaches or migraines, or the pain is unusually severe, it is recommended that you talk with your doctor.

14. It is not known if taking estrogen increases the risk of non-cancerous tumors of the pituitary gland (prolactinoma). Although prolactinoma is typically not life-threatening, it can damage vision and cause headaches. This will be monitored for at least three years when you start taking estrogen.
15. You are more likely to have dangerous side-effects from taking estrogen if you smoke, are overweight, are over 40 years old, or have a history of blood clots, high blood pressure, or a family history of breast cancer.
16. Taking estrogen will result in changes that will be noticeable by other people, and some trans people in similar circumstances have experienced harassment, discrimination, and violence, while others have lost support of loved ones. Your team can assist you in finding advocacy and support resources.
17. It is strongly advised not to take more estrogen than prescribed, as this increases health risks. Taking more estrogen than prescribed will not make feminization happen more quickly or increase the degree of change.
18. Since non-trans women go through menopause and stop making estrogen at about age 50, estrogen therapy for gender dysphoria is usually stopped at about the same time
19. The medical effects and safety of estrogen are not fully understood, and there may be long-term risks that are not yet known.

I agree to take estrogen as prescribed and to tell my care provider if I am not happy with the treatment or am experiencing any problems. I understand that the right dose or type of medication prescribed for me may not be the same as for someone else. I understand that physical examinations and blood tests are needed on a regular basis to check for negative side-effects of estrogen. I understand that estrogen can interact with other medications (including other sources of hormones), dietary supplements, herbs, alcohol, and street drugs. I understand that being honest with my care provider about what else I am taking will help prevent medical complications that could be life-threatening. I have been informed that I will continue to get medical care no matter what information I share. I understand that some medical conditions make it dangerous to take estrogen. I agree that if my doctor suspects I may have one of these conditions, I will be checked for it before the decision to start or continue estrogen is made. I understand that I can choose to stop taking estrogen at any time, and that it is advised that I do this with the help of my doctor to make sure there are no negative reactions to stopping. I understand that my doctor may suggest I reduce or stop taking estrogen, or switch to another type of feminizing medication, if there are severe side-effects or health risks that can't be controlled.

My signature below confirms that:

- My doctor has talked with me about the benefits and risks of estrogen, the possible or likely consequences of hormone therapy, and potential alternative treatment options.
- I understand the risks that may be involved.
- I understand that this form covers known effects and risks and that there may be long-term effects or risks that are not yet known.
- I have had sufficient opportunity to discuss treatment options with my doctor. All of my questions have been answered to my satisfaction.
- I believe I have adequate knowledge on which to base informed consent to the provision of estrogen.

Based on this, I wish to begin taking estrogen.

Parent #1 Signature	Date
Parent #2 Signature	Date
Physician's Signature	Date
Witness' Signature	Date

I understand that my parents have given permission for me to begin taking estrogen. I have had this consent form explained to me and agree to the estrogen treatment.

Patient's Signature	Date

INFORMED CONSENT FORM
LUPRON DEPOT® FOR GENDER DYSPHORIA: FEMALE TO MALE

I am receiving treatment for gender dysphoria. The cause of gender dysphoria is not known, but is thought to be partly due to genetic or environmental causes affecting the early development of my brain pathways. I understand that the effect of this on me means that, even though I think of myself partially or completely as male, I am genetically, biologically and physically female. I want to receive treatment that will help my body stop having the changes of female puberty, so that it will help to match my sense of myself (my gender identity). This will allow me time to continue my gender journey without having to worry about unwanted, permanent body changes.

With the understanding and consent of my parents/guardians, I will start taking Lupron Depot®, a type of medication called a gonadotropin-releasing hormone analog, to stop my body from going through the changes of female puberty. At the same time, my treatment also involves "talking therapy" (psychotherapy) to help me think about all the possible results and consequences of going part or all the way through the physical change, called "transition", from a female towards a male body.

I understand that while Lupron Depot® treatment will reduce my female hormones and prevent further female body changes, it will not make my body more masculine. I know that this treatment will not change my genetic sex (chromosomes), and it will not change my internal reproductive organs (ovaries, uterus, and vagina).

I understand that, although Lupron Depot® is a common treatment for children with precocious puberty, it is newer to being used in healthy young adolescents with gender dysphoria, and the long-term effects are not fully known. It has been explained to me that my doctors are suggesting and prescribing Lupron Depot® because they believe that this will allow me more time to explore my gender and other developmental issues. This may also facilitate my later physical transition by preventing the development of female sex characteristics (such as breasts, broad hips and menstrual periods) that are difficult or impossible to reverse if I continue on to pursue gender-affirming surgery. I may (or may not) decide down the road for partial or full physical transition to a male, perhaps eventually including testosterone therapy to cause male body changes and surgery to remove or reshape my internal and external female reproductive structures. However, taking Lupron Depot® now does not guarantee that I will eventually want, need, or have testosterone therapy and/or surgery. The decision to start testosterone therapy will be made jointly between me, my parents or caregivers, and my medical and mental-health doctors. Gender-affirming surgery has to be talked about in detail when I am further along in my transition, and final decisions can only be made after I have been living in the gender role that is congruent with my gender identity for a period of time.

There are also possible short- and long-term considerations and risks of Lupron Depot® use in natal females, as follows:

1. Lupron Depot® is not generally started in youth until their gender dysphoria has emerged or worsened with the earliest signs of puberty (called Tanner stage 2). In natal females, this means breast budding. As well, any co-existing psychological, medical, or social problems that could interfere with treatment must have been addressed prior to starting.

2. Lupron Depot® is given as an intramuscular (deep) injection in the thigh every 4 weeks; longer-acting forms can be given every 13 weeks. This can be given by the family doctor or a trained family member. The injections do cause some pain.

3. When patients take Lupron Depot, they need to have regular blood testing (generally, after 3 months, and then every 6-12 months), to ensure that the dosage of Lupron Depot® is correct. This may involve a 45-minute test with an IV.

Informed Consent Form: Lupron Depot® for Natal Females with Gender Dysphoria (continued)

4. In general, Lupron Depot® therapy is continued no longer than two years without stopping or adding in testosterone therapy.

5. If Lupron Depot® is not taken regularly as directed, it can actually cause a speeding-up of pubertal changes.

6. Lupron Depot® works fairly rapidly to reduce the estrogen to a very low level. This will halt the physical changes of female puberty, such as enlargement of the breasts, widening of the hips; and the onset of menstrual periods.

7. Lupron Depot® will not reverse some of the changes of female development that have already happened (breast size, width of hips). It will stop menstrual periods and cause vaginal dryness. It will reduce the sex drive.

8. While Lupron Depot® interferes with fertility, it does not affect the ability to get a sexually transmitted infection. Precautions against getting an STI must still be taken.

9. When Lupron Depot® is stopped, it is known that the puberty restarts within 3-6 months. To the best of our knowledge, there are no permanent effects on female fertility or ovarian/uterine/breast health if the Lupron Depot® is taken and stopped.

10. If Lupron Depot® is taken during the growth spurt, it will slow down the growth rate. In natal females, this may cause an overall small increase in the adult height, particularly if they later start on testosterone.

11. Lupron Depot® causes the calcium uptake by the bones, which is greatly increased during puberty, to slow down. For this reason, it is important that patients on Lupron Depot® take other measures to protect their bones: keeping active and ensuring good calcium and Vitamin D intake. It is not known if using Lupron Depot® increases the chance for osteoporosis in older age.

12. There is about a 5% (1 in 20) chance that a person taking Lupron Depot® can develop an allergy to the medication, which presents as a red, painful sterile abscess (boil) at the injection site. This may start out gradually and get worse with each injection. Rarely, the abscess will have to be drained by incision. If a person develops this problem, the Lupron Depot® must be stopped, and there may not be an alternate medication.

13. There may be long-term side-effects of Lupron Depot® that we do not yet know about.

I agree to take Lupron Depot® as prescribed and to tell my doctor if I am not happy with the treatment or am experiencing any problems. I understand that the right dose or type of medication prescribed for me may not be the same as for someone else. I understand that physical examinations and blood tests are needed on a regular basis to check for the effects of Lupron Depot®. I understand that Lupron Depot® can interact with other medications, dietary supplements, herbs, alcohol, and street drugs. I understand that being honest with my care provider about what else I am taking will help prevent medical complications that could be serious. I have been informed that I will continue to get medical care no matter what information I share. I understand that I can choose to stop taking Lupron Depot® at any time, and that it is advised that I do this with the help of my doctor to make sure there are no negative reactions to stopping. I understand that my doctor may suggest I stop taking Lupron Depot®, if there are severe side effects or health risks that can't be controlled.

My signature below confirms that:

- My doctor has talked with me about the benefits and risks of Lupron Depot® and potential alternative treatment options.
- I understand the risks that may be involved.
- I understand that this form covers known effects and risks and that there may be long-term effects or risks that are not yet known.
- I have had sufficient opportunity to discuss treatment options with my doctor. All of my questions have been answered to my satisfaction.
- I believe I have adequate knowledge on which to base informed consent to the taking Lupron Depot®.

Based on this, I wish to begin taking Lupron Depot®.

_____

Parent #1 Signature Date

_____

Parent #2 Signature Date

_____

Physician's Signature Date

_____

Witness' Signature Date

I understand that my parents have given permission for me to begin taking Lupron Depot®. I have had this consent form explained to me and agree to the Lupron Depot® treatment.

_____

Patient's Signature Date

INFORMED CONSENT FORM
TESTOSTERONE THERAPY FOR GENDER DYSPHORIA

I am receiving treatment for gender dysphoria. The cause of gender dysphoria is not known, but is thought to be partly due to genetic or environmental causes affecting the early development of my brain pathways. I understand that the effect of this on me means that, even though I think of myself partially or completely as male, I am genetically, biologically and physically female. I want to receive treatment that will help me change my body towards that of a male, so that it will match my sense of myself (my gender identity).

With the understanding and consent of my parents/guardians, I may have been taking a medicine called Lupron Depot® to stop me from going through puberty as a female. Regardless, my treatment also involves "talking therapy" (psychotherapy) to help me think about all the possible results and consequences of going part or all the way through the physical change, called "transition", from a female towards a male body.

I understand that I may now begin taking the male hormone testosterone, up to a dose that would be normal for males my age. I understand that testosterone will cause my body to become more masculine in appearance, and it will reduce my female hormones. This will probably mean that I will not menstruate (have "periods"), and that I will not be fertile (able to get pregnant) for the duration of treatment. I know that this treatment will not change my genetic sex (chromosomes), and it will not change my internal reproductive organs (ovaries, uterus, and vagina).

I understand that, although testosterone is a common treatment for adults with gender dysphoria, using this treatment in young adolescents is a newer development, and the long-term effects are not fully known. It has been explained to me that doctors are prescribing testosterone because they believe that I will continue towards full or partial physical transition to a male body, perhaps including eventual surgery to remove my inner female reproductive organs (ovaries and uterus). There is another kind of surgery to create male genitalia (penis and scrotum), that is also a separate decision. However, taking testosterone now does not guarantee that I will eventually want, need, or have these surgeries. Gender-affirming surgery has to be talked about in detail when I am further along in my transition, and final decisions can only be made after I have been living in the gender role that is congruent with my gender identity for a period of time.

There are also possible long-term considerations and risks of testosterone use in natal females, as follows:

1. The masculinizing effects of testosterone can take several months or longer to become noticeable, the rate and degree of change can't be completely predicted, and changes may not be complete for 2-5 years after starting testosterone.

2. The following changes will likely be permanent, even if testosterone is discontinued:
   - lower voice pitch (i.e., voice becoming deeper)
   - increased growth of hair, with thicker/coarser hairs, on arms, legs, chest, back, and abdomen
   - gradual growth of moustache/beard hair
   - hair loss at the temples and crown of the head, with the possibility of becoming completely bald
   - genital changes may or may not be permanent if testosterone is stopped; these include clitoral growth (typically 1-3 cm) and vaginal dryness

3. The following changes are usually not permanent (that is, they will likely reverse if testosterone is discontinued):
   - ' acne, which may be severe and can cause permanent scarring if not treated
   - fat may redistribute to a more masculine pattern (decreased on buttocks/hips/thighs, increased in abdomen—changing from "pear shape" to "apple shape")

- increased muscle mass and upper body strength
- increased libido (sex drive)
- menstrual periods typically stop within 1-6 months of starting testosterone

4. It is not known what the effects of testosterone are on fertility. Even if you stop taking testosterone, you may or may not be able to get pregnant in the future. Even after testosterone stops your menstrual periods, it may still be possible for you to get pregnant, and you must be aware of birth control options (if applicable). You must not take testosterone if you are pregnant. You still need to protect yourself from sexually transmitted infections,

5. There are some aspects of your body that will not be changed by testosterone:
   - breasts may appear slightly smaller due to fat loss, but will not substantially shrink
   - although voice pitch will likely drop, other aspects of speech will not become more masculine

6. Taking testosterone can cause changes that increase the risk of heart disease, including:
   - decreasing good cholesterol (HDL) and increasing bad cholesterol (LDL)
   - increasing blood pressure
   - increasing deposits of fat around the internal organs

7. The risks of heart disease are greater if people in the family have had heart disease, if you are overweight, or if you smoke. The doctor can provide you with advice about options to stop smoking.

8. Heart health check-ups, including monitoring of weight and cholesterol levels, should be done periodically as long as you are taking testosterone.

9. Taking testosterone can increase the red blood cells and hemoglobin, and while the increase is usually only to a normal male range (which does not pose health risks), a high increase can cause potentially life-threatening problems, such as stroke and heart attack. Your blood-cell count should be monitored periodically while you are taking testosterone.

10. Taking testosterone can increase the risk for diabetes by decreasing the body's response to insulin, causing weight gain, and increasing deposits of fat around the internal organs. Your fasting blood glucose should be monitored periodically while you are taking testosterone.

11. Testosterone can be converted to estrogen by various tissues in my body, and it is not known with certainty whether or not this increases the risks of ovarian, breast, cervical or uterine cancer.

12. Taking testosterone can lead to the cervix and the walls of the vagina becoming more fragile, and this can lead to tears or abrasions that increase the risk of sexually transmitted infections (including HIV) during vaginal sex—no matter the gender of the partner. Frank discussion with your doctor about your sexual practices can help determine how best to prevent and monitor for sexually transmitted infections. Some patients require the use of vaginal estrogen cream for this problem.

13. Taking testosterone can cause headaches or migraines. If you are frequently having headaches or migraines, or the pain is unusually severe, it is recommended that you talk with your doctor.

14. Taking testosterone can cause emotional changes, including increased irritability, frustration, and anger. Your doctor can assist you in finding resources to explore and cope with these changes.

15. Taking testosterone will result in changes that will be noticeable by other people, and some trans people in similar circumstances have experienced harassment, discrimination, and violence, while others have lost support of loved ones. Your team can assist you in finding advocacy and support resources.

16. It is strongly advised not to take more testosterone than prescribed, as this increases health risks. Taking more medication than prescribed will not make masculinization happen more quickly or increase the degree of change. Extra testosterone can be converted to estrogen, which may slow or stop masculinization.

17. Since non-trans men make testosterone their whole lives, testosterone therapy for gender dysphoria is generally continued lifelong.

18. The medical effects and safety of testosterone are not fully understood, and there may be long-term risks that are not yet known.

I agree to take testosterone as prescribed and to tell my doctor if I am not happy with the treatment or am experiencing any problems. I understand that the right dose or type of medication prescribed for me may not be the same as for someone else. I understand that physical examinations and blood tests are needed on a regular basis to check for negative side-effects of testosterone. I understand that testosterone can interact with other medications (including other sources of hormones), dietary supplements, herbs, alcohol, and street drugs. I understand that being honest with my doctor about what else I am taking will help prevent medical complications that could be life-threatening. I have been informed that I will continue to get medical care no matter what information I share. I understand that some medical conditions make it dangerous to take testosterone. I agree that if my doctor suspects I may have one of these conditions, I will be checked for it before the decision to start or continue testosterone is made. I understand that I can choose to stop taking testosterone at any time, and that it is advised that I do this with the help of my doctor to make sure there are no negative reactions to stopping. I understand that my doctor may suggest I reduce or stop taking testosterone if there are severe side-effects or health risks that can't be controlled.

My signature below confirms that:

- My doctor has talked with me about the benefits and risks of testosterone, the possible or likely consequences of hormone therapy, and potential alternative treatment options.
- I understand the risks that may be involved.
- I understand that this form covers known effects and risks and that there may be long-term effects or risks that are not yet known.
- I have had sufficient opportunity to discuss treatment options with my doctor. All of my questions have been answered to my satisfaction.
- I believe I have adequate knowledge on which to base informed consent to the provision of testosterone therapy.

Based on this, I wish to begin taking testosterone.

_____

Parent #1 Signature Date

_____

Parent #2 Signature Date

_____

Physician's Signature Date

_____

Witness' Signature Date

I understand that my parents have given permission for me to begin taking testosterone. I have had this consent form explained to me and agree to the testosterone treatment.

_____

Patient's Signature Date

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 29 March 2021
doi: 10.3389/fpsyt.2021.632784

A Follow-Up Study of Boys With Gender Identity Disorder

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This study reports follow-up data on the largest sample to date of boys clinic-referred for gender dysphoria ($n = 139$) with regard to gender identity and sexual orientation. In childhood, the boys were assessed at a mean age of 7.49 years (range, 3.33–12.99) at a mean year of 1989 and followed-up at a mean age of 20.58 years (range, 13.07–39.15) at a mean year of 2002. In childhood, 88 (63.3%) of the boys met the DSM-III, III-R, or IV criteria for gender identity disorder; the remaining 51 (36.7%) boys were subthreshold for the criteria. At follow-up, gender identity/dysphoria was assessed via multiple methods and the participants were classified as either persisters or desisters. Sexual orientation was ascertained for both fantasy and behavior and then dichotomized as either biphilic/androphilic or gynephilic. Of the 139 participants, 17 (12.2%) were classified as persisters and the remaining 122 (87.8%) were classified as desisters. Data on sexual orientation in fantasy were available for 129 participants: 82 (63.6%) were classified as biphilic/androphilic, 43 (33.3%) were classified as gynephilic, and 4 (3.1%) reported no sexual fantasies. For sexual orientation in behavior, data were available for 108 participants: 51 (47.2%) were classified as biphilic/androphilic, 29 (26.9%) were classified as gynephilic, and 28 (25.9%) reported no sexual behaviors. Multinomial logistic regression examined predictors of outcome for the biphilic/androphilic persisters and the gynephilic desisters, with the biphilic/androphilic desisters as the reference group. Compared to the reference group, the biphilic/androphilic persisters tended to be older at the time of the assessment in childhood, were from a lower social class background, and, on a dimensional composite of sex-typed behavior in childhood were more gender-variant. The biphilic/androphilic desisters were more gender-variant compared to the gynephilic desisters. Boys clinic-referred for gender identity concerns in childhood had a high rate of desistance and a high rate of a biphilic/androphilic sexual orientation. The implications of the data for current models of care for the treatment of gender dysphoria in children are discussed.

Keywords: gender dysphoria, gender identity disorder, gender non-conformity, sexual orientation, DSM-5

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: *24 November 2020*
Accepted: *18 February 2021*
Published: *29 March 2021*

Citation:
Singh D, Bradley SJ and Zucker KJ (2021) A Follow-Up Study of Boys With Gender Identity Disorder. Front. Psychiatry 12:632784. doi: 10.3389/fpsyt.2021.632784

INTRODUCTION

Gender identity is considered to be, for most people, a central aspect of one's sense of self (1–6).[1] By around 3 years of age, if not earlier, most children can self-label themselves as either a boy or a girl (11–14) although cognitive-developmental gender theory suggests that the understanding of gender as an "invariant" aspect of the self does not occur until early to middle childhood, with the achievement of concreate operational thought (12, 15, 16). Gender differences in the adoption of gender role behavior, i.e., behavior associated with cultural definitions of masculinity and femininity, also emerge during the preschool years, if not earlier. These behaviors span various domains, including peer, toy, role play, and activity preferences [e.g., (3, 17, 18)]. Normative developmental research has long documented that, on average, both gender identity and gender role behaviors show significant and substantial between-sex differences (19–21). Later in development, sexual orientation also shows a substantial between-sex difference, i.e., most males are sexually attracted to females and most females are sexually attracted to males (19, 22).

In the 1950s and 1960s, a small clinical literature began to describe the phenomenology of children who displayed marked gender-variant behavior, including the strong desire to be of the other gender [e.g., (23–27)]. Subsequent volumes by Stoller (28) and Green (29) provided more comprehensive descriptions of such children. These early works were the sequel to the introduction of the diagnostic term Gender Identity Disorder (GID) of Childhood to the psychiatric nomenclature in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-III; (30)], currently termed Gender Dysphoria (GD) in the DSM-5 (31). Since 1980, empirical research has examined a number of parameters pertaining to GID/GD: epidemiology, diagnostic and assessment methods, associated psychopathology, causal mechanisms, and therapeutic approaches [for reviews, see, e.g., (32–39)].

An additional parameter (the focus of the present study) pertains to the developmental course of GID in children. In the early literature, it was posited by some that pervasive gender-variant behavior in children might be a predictor of GID in adulthood (termed Transsexualism in the DSM-III) [e.g., (26, 40)]. At the same time, it was also recognized that gender-variant behavior in childhood was associated with sexual orientation (in males, androphilia, i.e., sexual attraction to men; in females, gynephilia, i.e., sexual attraction to women), but without co-occurring gender dysphoria [see, e.g., (41, 42); for a meta-analytic review, see (43)].

To date, there have been at least 10 follow-up studies of children whose behavior was consistent with the DSM diagnosis of GID (or GD per DSM-5) (44–53). Across these studies, the year at the time of first evaluation in childhood ranged from 1952 (49) to 2008 (51). For the 9 studies that included boys, the sample sizes (excluding those lost to follow-up) ranged from 6 to 79 (Mean age, 26 years). Most of these studies also provided the age at the time of first evaluation in childhood, which ranged from a mean of 7 years (47) to a mean of 9 years (48), with an age range from 4 to 12 years.

At the time of follow-up, using different metrics (e.g., clinical interview, maternal report, dimensional measurement of gender dysphoria, a DSM diagnosis of GID, etc.), these studies provided information on the percentage of boys who continued to have gender dysphoria (herein termed "persisters") and the percentage of boys who did not (herein termed "desisters").[2] Of the 53 boys culled from the relatively small sample size studies (Bakwin, Davenport, Kosky, Lebovitz, Money and Russo, Zuger), the percentage classified as persisters was 9.4% (age range at follow-up, 13–30 years). In Green (47), the percentage of persisters was 2% (total $n = 44$; Mean age at follow-up, 19 years; range, 14–24); in Wallien and Cohen-Kettenis (52), the percentage of persisters was 20.3% (total $n = 59$; Mean age at follow-up, 19.4 years; range, 16–28); and in Steensma et al. (51), the percentage of persisters was 29.1% (total $n = 79$; Mean age at follow-up, 16.1 years; range, 15–19). Across all studies, the percentage of persisters was 17.4% (total $N = 235$), with a range from 0 to 29.1%.[3]

These studies also provided information on the sexual orientation of the boys at the time of follow-up. In the early studies, sexual orientation was ascertained from various sources (e.g., open-ended interviews with the patient, parent-report, chart information, etc.). In the more recent studies, sexual orientation was assessed in a more systematic manner, such as the use of a structured interview to assign a Kinsey-based rating of sexual orientation in fantasy and a rating of sexual orientation in behavior, dummy coded where a 0 = gynephilia and a 6 = androphilia [e.g., (47)].

Of the 53 boys culled from the relatively small sample size studies (op. cit.), 13 (34.2%) of the patients were classified as gynephilic and 25 (65.8%) were classified as biphilic/androphilic.[4] In the remaining 15 patients (28.3% of the combined samples), their sexual orientation was either uncertain or unknown.

[1]In one study, Turner and Brown (7) found that school-age children rarely mentioned their gender when providing open-ended self-descriptions; the most frequent descriptor pertained to activities and preferences. Turner and Brown suggested that it might be the case that gender is so central to one's self-concept that it "goes without saying" (p. 709). In contemporary times in the West, a very small number of parents choose to not "gender" their children ("theybies") by not referring to them as boys or girls (and, at times, not even announcing to others the child's biological sex), dressing them in gender-neutral ways, etc. Little is known about the gender identity and gender role patterns of these children (8–10).

[2]The terms persistence and desistance have been used for a long time in clinical developmental psychiatry and psychology [e.g., (54)]. Zucker (55) was the first to apply these terms to describe the developmental psychosexual trajectories of children diagnosed with GID.

[3]The percentages provided here differ somewhat from other summary reviews [(39), pp. 285–286, (56, 57)] because we have excluded patients who were seen for the first time in adolescence [for this reason, data from Zuger (58) are also not included]. One other follow-up study was conducted by Nakamura (59). Unfortunately, this dissertation is not available for purchase at ProQuest (Ann Arbor, MI) and is only available for loan at the University of Essex library. Due to COVID-19 restrictions, it is currently inaccessible (K. Clarke, personal communication to G. Rieger, June 15, 2020). The director of the clinic at the time when the data were collected does not have a copy of the dissertation (D. Di Ceglie, personal communication, June 15, 2020).

[4]As pointed out by Reviewer 1, biphilic is a dubious neologism, combining Latin and Greek derivatives. Diphilic would be the more accurate derivative. However, introducing this term would probably confuse many readers, so we have retained the term biphilic (see https://en.wikipedia.org/wiki/Androphilia_and_gynephilia).

In Green's (47) study, 11 (25%) of the boys were classified as gynephilic (Kinsey ratings of 0–1) and 33 (75%) were classified as biphilic/androphilic in fantasy (Kinsey ratings of 2–6). For behavior, 6 (20%) were classified as gynephilic and 24 (80.0%) were classified as biphilic/androphilic. The remaining 14 boys (31.8% of the total sample) could not be classified with regard to behavior because they had had no interpersonal sexual experiences. In Green's study, the sexual orientation of a comparison group of boys, who had been recruited from the community, was also assessed: 100% of these boys ($n = 35$) were classified as gynephilic in fantasy and 96% ($n = 25$) were classified as gynephilic in behavior.

In the Wallien and Cohen-Kettenis (52) study, sexual orientation was assessed for attraction (2 items), fantasy (2 items), behavior (4 items), and sexual identity (1 item) using a self-developed Sexual Orientation Questionnaire. As in Green, Kinsey-type ratings were used in the analysis. Depending on the metric, data on sexual orientation were not available for anywhere between 22 and 40 (27.2–67.7%) patients. For attraction, 32% were classified as gynephilic and 68% were classified as androphilic (total $N = 37$); for fantasy, 19% were classified as gynephilic, 19% were classified as biphilic, and 62% were classified as androphilic (total $N = 21$); for behavior, 21% were classified as gynephilic, 16% were classified as biphilic, and 63% were classified as androphilic (total $N = 19$); lastly, for sexual identity, 19% were classified as gynephilic ("heterosexual"), 19% were classified as biphilic ("bisexual"), and 62% were classified as androphilic ("homosexual") (total $N = 27$). Steensma et al. (51) used the same metrics as Wallien and Cohen-Kettenis. Depending on the metric, data on sexual orientation were not available for anywhere between 25 and 40 (31.6%-50.6%) patients. For attraction, 19.2% were classified as gynephilic, 15.4% were classified as biphilic, and 65.4% were classified as androphilic (total $N = 52$); for fantasy, 14% were classified as gynephilic, 22% were classified as biphilic, and 64% were classified as androphilic (total $N = 50$); for behavior, 35.9% were classified as gynephilic, 12.8 were classified as biphilic, and 51.3% were classified as androphilic (total $N = 39$); lastly, for sexual identity, 13% were classified as gynephilic ("heterosexual"), 27.8% were classified as biphilic ("bisexual"), and 59.3% were classified as androphilic ("homosexual") (total $N = 54$).

In recent years, there have been various criticisms of these follow-up studies [see, e.g., (60–63); for a rebuttal, see (64)], particularly with regard to the putatively high percentage of desistance. It has been questioned, for example, to what extent the patients in these studies truly had GID/GD. For example, in the early studies, prior to the publication of DSM-III, one could reasonably argue that the diagnostic status of the patients was unclear because there were no formal diagnostic criteria to rely upon. However, one could argue in return that the behavior of these boys was phenomenologically consistent with the subsequent DSM criteria.

Consider, for example, the systematic study by Green [(47), Figure 1.2]. Green reported that 15% of the feminine boys, per parent-report, had "never" expressed the desire to be a girl or a woman at the time of the baseline assessment, 60% "occasionally" had such a desire, and only 25% had such a desire "frequently." Thus, a conservative critic might argue that only the last group would have met one of the key indicators for the GID/GD diagnosis in the DSM.[5] On the other hand, suppose a boy "occasionally" voiced the desire to be a girl over a period of several years. One might want to make the case that this would be consistent with the DSM descriptors of "persistently" or "repeatedly," etc. Of course, one could debate what would genuinely count as "occasionally" (in Green's trichotomous metric, it would be anything more than "never" and less than "frequently"). In any case, it is probably reasonable to argue that, in Green's study, some boys were threshold and some boys were subthreshold for the equivalent of a DSM diagnosis. Given that in Green's study only one boy persisted with gender dysphoria at the time of follow-up, the threshold-subthreshold distinction would not really matter.

Studies that employed DSM criteria for GID/GD allow for a more formal examination of the "No True Scotsman" argument (https://en.wikipedia.org/wiki/No_true_Scotsman).

In the Wallien and Cohen-Kettenis (52) study, the DSM-III-R criteria were used to diagnose GID. Of the 12 persisters, all met the criteria for GID at the time of the baseline assessment; in contrast, only 68% of the 47 desisters met the criteria for GID; the remainder were deemed subthreshold for the diagnosis. Thus, in their study, the threshold-subthreshold distinction appears to have been an important one in predicting outcome; nonetheless, it should be noted that 68% of the desisters had been threshold for the diagnosis in childhood—perhaps a strong rebuttal to the No True Scotsman argument. In Steensma et al. (51), the DSM-IV-TR criteria were used. Of the 23 persisters, 21 (91.3%) met the criteria for GID; in contrast, only 22 (39.3%) of the 56 desisters were threshold for the diagnosis, suggesting an even more substantial difference in the threshold-subthreshold distinction than was found in Wallien and Cohen-Kettenis. Although the latter percentage was lower than what was found in Wallien and Cohen-Kettenis, that almost 40% of the desisters met the criteria for GID in childhood still argues in favor that the children were desisting from something.[6]

From Wallien and Cohen-Kettenis (52) and Steensma et al. (51), one predictor of outcome, therefore, was the distinction between being threshold or subthreshold for the GID diagnosis in childhood. Dimensional measures of gender-variant behavior have also proven useful. In both Wallien and Cohen-Kettenis and Steensma et al., dimensional measures of sex-typed behavior in childhood also significantly discriminated between the persisters and desisters, with the former group having, on average, more severe gender-variant behavior at the time of the childhood

[5]The situation is compounded even further because in the DSM-IV, unlike in the DSM-III and DSM-III-R (65), the stated desire to be of the other gender was not a necessary criterion for the diagnosis [for the rationale, see (66), pp. 483–486]. In DSM-5, the desire to be of the other gender does not require explicit verbalization; the clinician is allowed leeway in drawing inferences based on other sources of information [see (67), pp. 904–905].

[6]In the follow-up study by Drummond et al. (46) of 25 girls from our clinic, the desistance rate was 88%. Of the 22 desisters, 13 (59.0%) met the DSM-III, III-R or IV criteria for GID. In Wallien and Cohen-Kettenis (52), of the 9 girls who desisted, 55.5% met the DSM-III-R criteria for GID. In Steensma et al. (51), of the 24 girls who desisted, 58.3% met the DSM-IV criteria for GID.

assessment. Steensma et al. found two other predictors of persistence: boys who were assessed at an older age and boys who had made either a partial or complete gender "social transition" [see (68–70)]. Of the 12 boys who had partially or completely transitioned prior to puberty, 10 (83.3%) were classified as persisters. In contrast, of the 67 boys who had not socially transitioned, only 13 (19.4%) were classified as persisters.

In the present study, we provide follow-up data with regard to both gender identity (persistence vs. desistance) and sexual orientation (gynephilia vs. biphilia/androphilia) on the largest sample of boys studied to date. Apart from providing percentage data on these two variables, which will be discussed in a comparative perspective in relation to the prior studies and the epidemiological literature, we also examine the predictors of outcome in relation to both demographic and sex-typed behavior measures (including whether or not the boys were threshold or subthreshold for GID) collected at the time of the baseline assessment in childhood.

METHOD

Participants

The participants were 139 boys ("birth-assigned males")[7] who, in childhood, had been referred to and then assessed in the Gender Identity Service, Child, Youth, and Family Program at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario between 1975 and 2009 (Mean year of assessment, 1989.36) and were adolescents or adults at follow-up (Mean year at follow-up, 2002.35).[8]

Participants entered the follow-up study through two methods of recruitment. The majority of participants (77%) were recruited for research follow-up. There were two main waves of participant recruitment through research contact, from 1986 to 1993 (n = 32) and then from 2009 to 2011 (n = 71). During the period of data collection, 32 patients re-contacted the service for clinical reasons (eight for gender dysphoria, six for sexual orientation, and 18 for heterogeneous concerns) [for details, see (77), Appendix E]. They were informed about the opportunity to participate in the follow-up study and subsequently completed the study protocol. The majority of the patient-initiated participants had contacted the clinic between the two main waves of research recruitment. Thus, from 1994 to 2008, the participants who entered the study were primarily those who had contacted the service for clinical reasons.

In the early wave of follow-up, a lower-bound age for participation was set at 14 years, but by the mid-1990s this was changed to a lower-bound age of 16 years. In total, 110 (79.1%) participants were at least 16 years of age and 29 (20.9%) were younger than 16. Across the entire period of data collection, eligible participants, after review of the medical chart, were contacted at random (other than the participants who had returned to the service for clinical reasons). Due to lack of study resources and time constraints, contact with 162 other eligible participants was not attempted.

In total, 145 patients were approached about the follow-up study, either through research contact (n = 113) or following their clinical involvement with the Gender Identity Service (n = 32). Six patients declined, which yielded a participation rate of 95.9%. For those recruited for research purposes, initial contact, by telephone, letter or email, was first made with the parents because the patients were minors at the time of the childhood assessment and may have had no recollection of their clinic attendance. A total of 19 (14.3%) potential participants could not be reached/traced through previous addresses, registrars, and personal contacts.

Of the 139 participants, 110 were seen for a face-to-face assessment. For various reasons, the remaining 29 patients could not be seen for the face-to-face assessment (e.g., lived in another province or country, "too busy," severe mental health issues). For some patients, they provided some information over the phone or information was provided by the parents; thus, for these patients, it was possible to obtain some follow-up data about their gender identity and sexual orientation.

The demographic characteristics of the participants, including their age at assessment in childhood and at the time of follow-up, are shown in **Table 1**. The GID diagnosis in childhood was based on the DSM-III (n = 53), DSM-III-R (n = 46), or DSM-IV (n = 40) criteria applicable at the time of assessment.[9] A total of 88 (63.3%) boys met complete DSM criteria for GID in childhood. The remaining 51 (36.7%) boys were subthreshold for a DSM diagnosis, but all had some indicators of GID, and, based on the historical information provided during the assessment, some would have met the complete DSM criteria at some point in their lives prior to their assessment in childhood.[10] The percentage who met the complete DSM criteria for GID did not differ significantly as a function of DSM edition, $\chi^2_{(2)} < 1$.

Procedure

The majority of participants who completed the face-to-face assessment were evaluated on a single day. Three participants were seen twice. In these instances, the participants completed the self-report measures during their second visit as the complexity of their clinical presentation extended the duration of the assessment. Participants were provided a stipend for their participation in the follow-up assessment and reimbursement for travel expenses. For participants followed-up prior to 2009 (n = 68), the data were collected by the third author; for those followed-up between 2009 and 2011, the data were collected

[7]Two reviewers asked why we chose to use the noun "boys" instead of the noun "males." In our view, the question was reasonable but also a matter of semantics and taste. The third edition of *The Oxford Dictionary of Current English* (71) defines boy as "a male child..." Thus, we believe that the two words can be used synonymously. Males can refer to any age in the life-span whereas boys connote childhood. The participants in our study were coded as male at the time of their birth in the hospital delivery record, of which we had the actual birth records for the majority of the participants in the current study (72). As per Bouman et al. (73), one would say that the participants were "assigned male at birth" and then declared socially to be "boys" (74).

[8]The clinic was established in 1975 at the Clarke Institute of Psychiatry (75, 76), which became part of the CAMH in 1998.

[9]For boys seen prior to the publication of DSM-III in 1980, the draft criteria were used.

[10]In DSM-III, termed Atypical Gender Identity Disorder; in DSM-III-R and DSM-IV, termed Gender Identity Disorder Not Otherwise Specified.

TABLE 1 | Demographic characteristics ($N = 139$).

Characteristic	*M*	*SD*	Range	%
From childhood				
Age (in years)	7.49	2.66	3.33–12.99	
Year of birth	1981.87	7.50	1966–1996	
Year of assessment	1989.36	7.50	1975–2004	
IQ[a]	105.93	15.47	69–138	
Social class[b]	40.74	15.15	8.0–66.0	
Marital status[c]				
Two-parent family				64.7
Other				35.3
Caucasian				84.9
At follow-up				
Age (in years)	20.58	5.22	13.07–39.15	
Year of follow-up	2002.35	9.08	1986–2011	
Follow-up interval (in years)[d]	12.88	6.07	2.77–29.29	
IQ[e,f]	105.88	16.03	65–138	

[a]*Full-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.*
[b]*Hollingshead's (78) Four Factor Index of Social Status (absolute range, 8–66).*
[c]*Other included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.*
[d]*Interval denotes the time between childhood assessment and follow-up assessment.*
[e]*Full Scale IQ estimated using four subtests: Vocabulary, Comprehension, Block Design, and Object Assembly.*
[f]*An IQ score was available only for participants who completed the face-to-face assessment. Of these, scores were not available for one participant.*

by the first author ($n = 71$). The study was approved by the Institutional Review Boards at the Clarke Institute of Psychiatry (subsequently the Centre for Addiction and Mental Health; Protocol #198/2008–2011) and the University of Toronto.

Measures

Below, we describe the measures from assessment and follow-up of relevance for this article. A list of all measures used in the follow-up study can be found in Singh [(77), Table 4].

Childhood Assessment

Cognitive Functioning

Based on the child's age at the time of assessment, the appropriate version of the Wechsler Intelligence Scale for Children was administered (WPPSI-R or the WISC-R/WISC-III/WISC-IV). Full scale IQ scores were used to characterize level of cognitive functioning.

Behavioral and Emotional Problems

Parents completed the Child Behavior Checklist (CBCL), a measure of behavioral and emotional problems (79). Although not the focus of the present study, it is noted here because we used three CBCL indices (sum of all behavior problems and Internalizing and Externalizing *T* scores) as part of an internal validity analysis when comparing participants vs. non-participants (see Results).

Sex-Typed Behavior

Five child informant and two parent informant measures were used to assess the participants' sex-typed behavior in childhood: (1) Draw-a-Person [DAP] test (80); (2) a free-play task (81); (3) the Playmate and Playstyle Preferences Structured Interview (PPPSI) (82, 83); (4) sex-typed responses on the Rorschach test (84); (5) the Gender Identity Interview for Children (GIIC) (85–87); (6) the Gender Identity Questionnaire for Children (GIQC) (88–90); and (7) a measure of activity level/extraversion [(39); see also (91)]. These child and parent informant measures all have established discriminant validity, that is, they significantly differentiated the boys clinic-referred for gender identity concerns from control boys [for reviews, see (18, 92)]. A Childhood Sex-Typed Behavior Composite was subsequently computed for each participant (see below).

Follow-Up Assessment

Cognitive Functioning

Four subtests from the age-appropriate version of the Wechsler Intelligence Scales were administered (Vocabulary, Comprehension, Block Design, and Object Assembly). The standard scores from the subtests were averaged to form a prorated IQ score for cognitive functioning (93).

Concurrent Gender Identity

Concurrent gender identity was evaluated using a semi-structured interview and self-report questionnaires. During an audiotaped interview, each participant was asked to describe their current feelings about being a biological male. They were also asked to describe positive and negative aspects about their gender identity. For example, participants who reported a "male" gender identity were asked to describe positive and negative aspects of being male. The semi-structured interview also included questions based on the adolescent and adult GID criteria outlined in the DSM-III-R or DSM-IV (65, 94). Participants were asked to respond to these questions according to the last 12 months with *No, Sometimes,* or *Yes* [for details, see (77), Appendix G].

Two self-report measures were also used to assess current gender identity and gender dysphoria: (1) The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA) (95–97) or (2) the Gender Dysphoria/Identification questionnaire (GDIQ) (98). The GDIQ was developed prior to the GIDYQ-AA. As such, the GIDYQ-AA was introduced to the protocol subsequent to the GDIQ and, as a result, the more recent participants completed the GIDYQ-AA while earlier participants completed the GDIQ.

The male version of the GIDYQ-AA was completed. This 27-item questionnaire measures gender identity and gender dysphoria in adolescents or adults; participants over the age of 17 completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" are used instead of "boy" and "girl." Each item was rated on a 1–5 point response scale with verbal anchor points ranging from *Never* to *Always* based on a time frame of the past 12 months. Coding was such that a "lower" score signified more gender dysphoria. Item examples include the following:

"In the past 12 months, have you felt unhappy about being a man?" and "In the past 12 months, have you had the wish or desire to be a woman?" Principal axis factor analysis identified a one-factor solution that accounted for 61.3% of the variance. All factor loadings were ≥0.30 (median, 0.86; range, 0.34–0.96). The GIDYQ-AA has strong evidence for discriminant validity and a high threshold for specificity (i.e., low false positive rate for non-GID individuals) [see (95, 96, 99–102)].

The GDIQ (98) contains 8 items pertaining to gender identity and gender dysphoria. Factor analysis identified two factors, accounting for 31.4 and 12.5% of the variance, respectively (all factor loadings ≥0.45). Factor 1 consisted of five items pertaining to gender dysphoria and Factor 2 consisted of three items pertaining to gender role identification. For the present study, only the questions for Factor 1 were used. Each item was rated on a 3-point or 5-point scale for the past 12 months (see **Appendix 1** in **Supplementary Material**).

Participants were classified as having persistent gender dysphoria if their mean score on the GIDYQ-AA was ≤3.00, in line with sensitivity and specificity analyses from other data sets (95, 96). For participants who did not complete the GIDYQ-AA, the GDIQ was used. A participant was classified as a persister if two or more of the following five items on the GDIQ were endorsed: wish to have been born a girl (Item 1), wish to have surgery to change body (Item 2), feel more like a girl than a boy (Item 3), wonder if would be happier as a girl (Item 4), and somewhat or very dissatisfied with being a boy (Item 5).

Information regarding participants' gender identity/gender dysphoria was also obtained during the semi-structured clinical interview and, therefore, allowed for cross-validation of these questionnaire data. For those participants who did not complete the face-to-face interview, clinical information regarding gender identity/gender dysphoria was obtained through self- or parent-report or chart review. Across the entire sample, the GIDYQ-AA was used to classify persistence or desistence for 64 participants, the GDIQ for 42 participants, and interview/chart data/parent report for 33 cases.

Sexual Orientation

Sexual orientation in fantasy was assessed with specific questions from an audiotaped face-to-face interview and the self-report Erotic Response and Orientation Scale (EROS) (103).

The interview asked about four types of sexual fantasy over the past 12 months: (1) crushes on other people; (2) sexual arousal to visual stimuli (e.g., acquaintances, partners, and individuals from movies, television, etc.); (3) sexual content of night dreams; and (4) sexual content of masturbation fantasies. During the interview, participants were not asked directly about the gender of the person or persons who elicited sexual arousal, thus allowing time for the participant to provide this information spontaneously. Directed questions about the gender of the person(s) who elicited sexual arousal were asked only if the participant did not volunteer specific information about whether their arousal was directed to same-sex or opposite-sex individuals, or both. By the end of the interview, each participant provided information about sexual arousal to both same-sex and opposite-sex individuals. Using the Kinsey scale criteria (104), the interviewer assigned Kinsey ratings that ranged from 0 (exclusively gynephilic in fantasy) to 6 (exclusively androphilic in fantasy) for each question. A dummy score of 7 denoted that the participant did not experience or report any fantasies. A global fantasy score was also derived based on ratings from the four questions. Kinsey ratings for sexual orientation in fantasy were available for 129 participants.

Inter-rater reliability on Kinsey ratings for sexual orientation in fantasy was examined for 29 participants, selected at random. The second scorer listened to the audio recordings of the semi-structured interview, with specific attention to the information collected on sexual orientation. The inter-rater agreement on the Kinsey global fantasy rating was very good (kappa = 0.95) and the kappa values for the four specific components ranged from 0.81 to 1.00.

The EROS is a 16-item self-report measure assessing sexual orientation in fantasy over the past 12 months. Half of the questions pertained to gynephilic fantasy (e.g., "How often have you noticed that you had sexual feelings [even the slightest] while looking at a woman?") and the other half pertained to androphilic fantasy (e.g., "How often have you noticed that you had sexual feelings [even the slightest] while looking at a man?"). Participants who were 18 years and older completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" were used instead of "boy" and "girl." Each item was rated on a 5-point scale for frequency of occurrence, ranging from 1 ("none") to 5 ("almost every day"). Mean androphilic and gynephilic fantasy scores were derived for each participant. In the present study, we calculated a difference score between the participants' mean androphilic and gynephilic scores. Previous use of the EROS has shown good evidence of discriminant validity (98, 101).

Sexual orientation in behavior was assessed with specific questions during the face-to-face interview and with a modified version of the Sexual History Questionnaire (SHQ) (105). In the interview, questions asked about five types of sexual behavior: (1) dating; (2) holding hands in a romantic manner; (3) kissing; (4) genital fondling or touching a woman on the breasts, and (5) intercourse (penile-vaginal and anal). Kinsey ratings for behavior in the past 12 months were made in the same manner as fantasy ratings. Kinsey ratings for sexual orientation in behavior were available for 108 participants. Inter-rater reliability on Kinsey ratings for sexual orientation in behavior was examined for the same 29 participants. There was perfect inter-rater agreement on the Kinsey global behavior rating (kappa = 1.0) and the kappa values for the five specific components ranged from 0.91 to 1.00.

The modified SHQ consists of 20 questions. Ten questions pertained to gynephilic experiences (e.g., "How many women have you kissed on the lips in a romantic way?") and 10 questions pertained to androphilic experiences (e.g., "How many men have you kissed on the lips in a romantic way?"). Participants who were 18 years and older completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" were used instead of "boy" and "girl." Each item was rated on a 5-point scale for frequency

of occurrence, ranging from 1 ("none") to 5 ("11 or more"), based on a time frame of the past 12 months. Mean total scores for gynephilic and androphilic experiences were derived. In the present study, we calculated a difference score between the participants' mean androphilic and gynephilic scores.

On the basis of Kinsey ratings, participants who completed the face-to-face interview were classified, similar to Green (47), into the following three sexual orientation groups for both fantasy and behavior: (1) gynephilic (Kinsey global ratings of 0–1); (2) biphilic/androphilic (Kinsey global ratings of 2–6), and (3) no sexual fantasy or behavior.

Social Desirability

Social desirability refers to the desire to cast a favorable impression on others. It can threaten the validity of self-report scales if in answering questions respondents seek social approval or try to represent themselves in a favorable manner (106). People scoring high on social desirability tend to provide socially acceptable answers regardless if their response accurately describes them. Participants 18 years and older completed the Marlow-Crowne Social Desirability Scale (M-CSDS) (107), which consists of 33 true-false items. The scale contains 18 culturally acceptable but unlikely statements keyed in the true direction and 15 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 33. Participants 17 years and under were given a shorter version of the M-CSDS (108), containing 20 items that consist of 12 culturally acceptable but improbable statements keyed in the true direction and eight socially undesirable but probable statements keyed in the false direction for a maximum possible score of 20. For the present study, the percentage of endorsed socially desirable items was calculated for each participant. In order to integrate the data from both versions of the M-CSDS, participants' percentage score on each measure was converted to a proportion score which ranged from 0 to 1, which was used in all analyses. A higher proportion score indicates a greater propensity to give socially desirable responses. Several studies have found that the MCSDS is a reliable and valid measure of social desirability (107, 109, 110).

RESULTS

Preliminary Analyses

Participants vs. Non-participants

Given that not all eligible participants were seen for follow-up, it is important to see to what extent the participants vs. non-participants were similar with regard to baseline characteristics, in part to gauge the internal validity of the sample (111).

The non-participants consisted of three subgroups: (1) patients who were eligible to participate in the study but were not contacted ($n = 163$), (2) patients who declined to participate ($n = 6$), and (3) patients who were not successfully traced ($n = 19$). Two sets of analyses were conducted to compare study participants vs. non-participants. First, the participants were compared to the patients who were eligible but not contacted. Second, the participants were compared to those who declined to participate and to those where contact was attempted but not successfully traced. Group comparisons were conducted on five demographic variables (age at assessment in childhood, IQ, ethnicity, and parents' marital status and social class), parent-report of behavior problems on the CBCL (three indices), and nine measures of childhood sex-typed behavior.

Of these 17 variables, there was only one significant difference between the 139 boys in the study compared to the 163 boys who were eligible to participate but were not contacted: participants had a higher IQ than non-participants, $t_{(289)} = 2.01$, $p = 0.046$.[11] The effect size for this comparison was small (unpooled $d = 0.22$) [for details, see (77), Tables 5, 6]. When compared to the six cases where participation in the study was declined and to the 19 cases where the families could not be traced, there was also only one significant difference: parent's marital status, $\chi^2_{(2)} = 9.02$, $p = 0.011$. The participants did not differ significantly from the non-participants who refused; however, they differed significantly from the cases that could not be traced, $\chi^2_{(1)} = 6.39$, $p = 0.012$. The participants were more likely to have originated within a two-parent household than those who could not be traced. The comparison between the non-participants who refused and those who could not be traced approached significance ($p = 0.056$, Fisher's exact test). Again, the non-participants who could not be traced were more likely to have come from a family composition that was not two-parent. A further summary of comparisons between the participants and those who declined or could not be traced can be found in the **Supplementary Material**.

Participants: Method of Recruitment

Using *t*-tests or chi-square tests, the 107 participants who entered the study through research contact were compared to the 32 participants who were recruited into the study after they had re-contacted the clinic for clinical reasons on the demographic variables, CBCL behavior problems in childhood, and the measures of childhood sex-typed behavior. There were no significant differences between the two groups on the demographic variables of age at assessment, ethnicity or parents' social class and marital status ($ps > 0.05$). The comparison on childhood IQ approached significance, $t_{(137)} = 1.97$, $p = 0.051$, with the research entry participants having, on average, a higher IQ than the clinical entry participants. On the CBCL, there was a significant difference on Internalizing problems only, $t_{(137)} = -2.02$, $p = 0.046$, with the clinical entry participants rated by their parents as having more internalizing problems compared to the research entry participants. Of the nine measures of childhood sex-typed behavior, the two groups differed significantly on three: (1) free play, $t_{(119)} = -2.11$, $p = 0.037$, (2) the Gender Identity Interview for Children, $t_{(83)} = -2.09$, $p = 0.04$, and (3) the Gender Identity Questionnaire for Children, $t_{(95)} = 2.39$, $p = 0.019$, with the clinical entry participants having, on average, more childhood cross-gender behavior than the research entry participants. The percentage of clinical entry participants who were threshold for the diagnosis of GID in childhood did not differ significantly from the research entry participants (75.8 vs. 59.8%), $\chi^2_{(1)} = 1.83$. Of the 32 clinical entry participants, 8 had re-contacted the clinic because

[11] IQ data were not available for 11 of the 163 boys who were eligible for the study but were not contacted.

of gender dysphoria. The above-described comparisons were repeated to compare the research and clinical entry participants but with these 8 participants excluded. With the eight participants who contacted the clinic for gender dysphoria removed, there were no significant group differences on demographic variables, CBCL behavior problems, and measures of childhood sex-typed behavior (all $ps > 0.05$).

Gender Identity at Follow-Up

Appendix 2 in Supplementary Material shows the follow-up data for gender identity and sexual orientation for each participant. Of the 139 participants, 17 (12%) were classified as persisters and the remaining 122 (88%) were classified as desisters. The age at the time of follow-up did not differ significantly between the persisters (Mean, 20.12 years; SD = 5.54) and desisters (Mean, 20.64 years; SD = 5.19), $t_{(137)} < 1$. Of the 107 participants who, for research purposes only, were contacted for the follow-up study, 10 (9%) were classified as persisters; of the 32 participants who were recruited into the study after they were seen for some type of clinical concern, 7 (22%) were classified as persisters. The difference in persistence rate as a function of recruitment entry type was not significant, $\chi^2_{(1)} = 2.53$, $p = 0.112$. The difference in persistence rate between those patients seen for the face-to-face assessment vs. those who were not (14.5 vs. 3.4%) was also not significant, $\chi^2_{(1)} = 1.70$, $p = 0.192$. **Supplementary Table 1** summarizes information on some domains of gender role outcome for the 17 participants classified as having persistent gender dysphoria.

For the 42 participants where the GDIQ was used to determine gender identity status at follow-up, four were classified as persisters and 38 were classified as desisters. Of the 38 desisters, three endorsed one item and the remainder endorsed none of the items.[12] The four participants classified as persisters endorsed between three and five items.

For the 64 participants where the GIDYQ-AA was used to determine gender identity status at follow-up, 12 were classified as persisters and 52 were classified as desisters. All 52 desisters had a mean score >3.00 on the GIDYQ-AA. Of the 12 persisters, 10 had a mean score ≤3.00 and two had mean scores that were >3.00. In spite of having mean scores on the GIDYQ-AA that were above the recommended cutoff for caseness (95), these two participants were considered persisters because their clinical interview data indicated that they were experiencing significant gender dysphoria. Thus, clinical judgment was used to make the final classification for these two participants.

For the remaining 33 participants, clinical interview, parent-report or chart data were used to classify the percentage who were persisters ($n = 1$; 3%) or desisters ($n = 32$; 97%).

The persistence rate of gender dysphoria was examined as a function of participants' GID diagnostic status in childhood (threshold vs. subthreshold). Of the 88 participants who met the full diagnostic criteria for GID in childhood, 12 (13.6%) were classified as persisters and the remaining 76 (86.4%) were not. Of the 51 participants who were subthreshold for the GID diagnosis in childhood, 5 (9.8%) were classified as persisters and the remaining 46 (90.2%) were not. A chi-square analysis indicated that the rate of persistence did not differ significantly between the threshold and subthreshold groups, $\chi^2_{(1)} < 1$.

Over the years, prevalence rates for gender dysphoria in adults have varied considerably. The variation is likely a function of many factors, including definition, time period, and source of ascertainment. For example, in the Standards of Care of the World Professional Association for Transgender Health (112), probably relying on an estimate given in the DSM-IV-TR, the prevalence of gender dysphoria in adult males was estimated to be 1 in 30,000. In the meta-analysis by Arcelus et al. (113), the prevalence in adult males was estimated at 1 in 14,705. Lastly, Zhang et al.'s (114) review of recent population-based surveys estimated the prevalence of a self-reported transgender identity in adults to range between 0.33 and 0.53% (males and females combined). Regardless of which base rate figure one might choose to use as a point of comparison, the persistence rate of 12% (while low in an absolute sense) would be considerably higher than what one would detect in the general population.

Sexual Orientation at Follow-Up

Table 2 shows the Kinsey ratings for sexual orientation in fantasy. Data were not available for 10 participants, all of whom were desisters with regard to gender dysphoria. Based on the global rating for sexual orientation in fantasy, 43 (33.3%) participants were classified as gynephilic in fantasy and 82 (63.6%) were classified as biphilic/androphilic in fantasy. In the remaining four (3.1%) cases, the participants were classified as having no sexual fantasies and, therefore, a Kinsey rating could not be assigned.[13] In all four cases, the participants were desisters. Of the 17 participants classified as persisters, 1 (5.9%) was gynephilic in fantasy and 16 (94.1%) were biphilic/androphilic in fantasy. For participants assigned a Kinsey rating between 0 and 6 in fantasy, we correlated the interviewer's Kinsey rating with the participants' responses on the EROS in which their mean gynephilic score was subtracted from their mean androphilic score. This yielded an $r(101) = 0.86$, $p < 0.001$.

Table 2 also shows the Kinsey ratings for sexual orientation in behavior. Data were available for 108 participants. Based on the global rating for sexual orientation in behavior, 29 (26.9%) participants were classified as gynephilic and 51 (47.2%) were classified as biphilic/androphilic. The remaining 28 (25.9%) participants did not report any sexual behaviors in the 12 months preceding the follow-up assessment. For participants assigned a Kinsey rating between 0 and 6 in behavior, we correlated the

[12] By "endorsed," we mean that the participants answered other than "never" on Items 1–4 or response options d-e for Item 5 (see **Appendix 1** in Supplementary Material).

[13] For 104 participants, the Kinsey rating in fantasy was based on the information provided in the face-to-face interview. For 21 other participants, the Kinsey rating in fantasy was based on self-report (by telephone), information available in the participant's health record, or parent-report. Participants were assigned a Kinsey rating of 6 if the participant self-identified as "gay" or if the health record indicated that the patient was "homosexual" or gay, etc. Participants were assigned a Kinsey rating of 0 if the patient self-identified as "straight" or "heterosexual," etc. A chi-square test showed that the percentage of participants who were classified as Kinsey 0–1 vs. 2–6 did not differ significantly as a function sexual orientation ascertainment method, $\chi^2_{(1)} = 1.49$.

TABLE 2 | Kinsey ratings for sexual orientation in fantasy and behavior.

Variable	Kinsey rating (fantasy)[a]															
	0		1		2		3		4		5		6		No fantasy	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Crush	36	36.7	0	0	2	2.0	4	4.1	2	2.0	11	11.2	29	29.6	14	14.3
Visual	31	31.6	1	1.0	2	2.0	10	10.2	3	3.1	12	12.2	29	29.6	10	10.2
Dreams	13	13.3	1	1.0	1	1.0	4	4.1	3	3.1	3	3.1	27	27.6	46	46.9
Masturbation	21	21.9	2	2.1	3	3.1	6	6.3	2	2.1	7	7.3	33	34.4	22	22.9
Global fantasy rating	40	31.0	3	2.3	3	2.3	8	6.2	2	1.6	14	10.9	55	42.6	4	3.1
	Kinsey rating (behavior)[a]															
	0		1		2		3		4		5		6		No sexual behavior	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Holding hands	26	26.3	0	0	0	0	5	5.1	1	1.0	1	1.0	35	35.4	31	31.3
Kissing	21	21.2	0	0	0	0	6	6.1	2	2.0	2	2.0	34	24.3	34	34.3
Genital/breast contact	13	13.1	0	0	0	0	3	3.0	2	2.0	1	1.0	35	35.4	45	45.5
Intercourse	8	8.2	0	0	0	0	3	3.1	2	2.0	0	0	27	27.6	58	59.2
Global behavior rating	28	25.9	1	0.9	0	0	4	3.7	3	2.8	1	0.9	43	39.8	28	25.9

[a]*0 = Exclusively gynephilic to 6 = Exclusively androphilic.*

interviewer's Kinsey rating with the participants' responses on the SHQ in which their mean gynephilic score was subtracted from their mean androphilic score. This yielded an $r(75) = 0.79$, $p < 0.001$.

For those participants who could be assigned a Kinsey rating (i.e., excluding those participants who did not report any sexual fantasies or behavior or for whom data were not available), the correlation between Kinsey global fantasy and global behavior ratings was very strong, $r(78) = 0.92$, $p < 0.001$.

Group Classification as a Function of Gender Identity and Sexual Orientation in Fantasy at Follow-Up[14]

Combining gender identity (i.e., persister or desister) and sexual orientation in fantasy (i.e., gynephilic or biphilic/androphilic) at follow-up, the participants were classified into one of four outcome groups (for which we had all of the relevant data): (1) persistence of gender dysphoria with a biphilic/androphilic sexual orientation ($n = 16$); (2) desistance of gender dysphoria with a biphilic/androphilic sexual orientation ($n = 66$); (3) desistance of gender dysphoria with a gynephilic sexual orientation ($n = 42$); and (4) persistence of gender dysphoria with a gynephilic sexual orientation ($n = 1$). The participants who reported no sexual fantasies ($n = 4$) could not be included in this outcome classification. Given that only one participant was classified as gender dysphoric with a co-occurring gynephilic sexual orientation (Group 4), this category was excluded from subsequent analyses that compared these outcome groups.

[14]Given the strong correlation between Kinsey fantasy and behavior ratings and that there were fewer missing data on the Kinsey fantasy variable, participants were classified into one of the four outcome groups based on their fantasy ratings.

Demographic Characteristics in Childhood as a Function of Gender Identity and Sexual Orientation in Fantasy

Table 3 shows the demographic variables in childhood as a function of group. One-way ANOVAs and chi-square were conducted to evaluate whether the outcome groups differed on these variables. The groups differed significantly on four of the five childhood demographic variables. Duncan's multiple range test for unequal Ns showed that the biphilic/androphilic persisters were, on average, significantly older at the time of the childhood assessment than both the gynephilic desisters and the biphilic/androphilic desisters, who did not differ significantly from each other. The biphilic/androphilic desisters had, on average, a higher IQ than the biphilic/androphilic persisters but did not differ significantly from the gynephilic desisters. There was no significant difference in childhood IQ score between biphilic/androphilic persisters and gynephilic desisters. The biphilic/androphilic persisters were significantly more likely to come from a lower social class background compared to the gynephilic desisters and the biphilic/androphilic desisters, who did not differ significantly from each other (see also **Figure 1**). The biphilic/androphilic desisters were more likely to be living with both parents compared to the biphilic/androphilic persisters. There was no significant difference on marital status between the two desister groups.

The demographic variables from childhood on which the three groups differed–age at assessment, IQ, social class, and marital status–were significantly correlated (*r*s ranged from |0.32–0.58|) [see Table 12 in (77)]. To evaluate the predictive status of these variables on group outcome at follow-up, a multinomial logistic regression was performed. **Table 4** shows the results. For these analyses, the biphilic/androphilic desisters served as the reference

TABLE 3 | Demographic characteristics as a function of group.

Variable		Group			*F* or χ^2	*p*	η^2 or Cramer's V
		Persisters Biphilic/ Androphilic ($n = 16$)	Desisters Biphilic/ Androphilic ($n = 66$)	Desisters Gynephilic ($n = 42$)			
Childhood							
Age (in years)	*M*	8.85	6.96	7.49	3.57	0.031	0.06
	SD	1.67	2.69	2.62			
IQ[a]	*M*	101.63	110.20	103.18	3.77	0.026	0.06
	SD	14.81	14.56	15.16			
Social class[b]	*M*	23.76	44.97	39.44	15.30	<0.001	0.20
	SD	10.22	13.64	15.91			
Marital status[c]							
Two-parent	*N* (%)	7 (43.8)	49 (74.2)	24 (57.1)	6.74	0.034	0.23
Other	*N* (%)	9 (56.3)	17 (25.8)	18 (42.9)			
Ethnicity							
Caucasian	*N* (%)	14 (87.5)	58 (87.9)	32 (76.2)	2.77	0.250	0.14
Other	*N* (%)	2 (12.5)	8 (12.1)	10 (23.8)			
Follow-up							
Age at follow-up (in years)[d]	*M*	20.32	22.13	17.85	10.41	<0.001	0.15
	SD	5.67	4.97	3.95			
IQ at follow-up[a,e,f]	*M*	99.07	110.47	104.19	3.82	0.025	0.07
	SD	16.29	13.54	17.50			
Follow-up interval (in years)	*M*	11.47	15.17	10.36	9.63	<0.001	0.04
	SD	6.77	6.03	4.85			
Social desirability[g]	*M*	0.44	0.43	0.52	3.07	0.051	0.07
	SD	0.17	0.18	0.19			

[a] *Full-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.*
[b] *Hollingshead's (78) Four Factor Index of Social Status (absolute range, 8–66).*
[c] *Other included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.*
[d] *Interval denotes the time between childhood assessment and follow-up assessment.*
[e] *Full Scale IQ was estimated using four subtests: Vocabulary, Comprehension, Block Design, and Object Assembly.*
[f] *An IQ score was available only for participants who completed the face-to-face assessment.*
[g] *Absolute range, 0.00–1.00. Higher score indicates a greater propensity to give socially desirable responses. Age at follow-up, IQ at follow-up, social class, and parent's marital status were co-varied.*

group. Each coefficient, *B*, represents the change in the log odds for Group for a 1-unit increase in the corresponding predictor, controlling for all other predictors in the model. The next column presents the standard error (SE) for each *B*. The Wald statistic was the quantity used to determine the significance level of each predictor variable. The quantity, e^B, is the multiplicative change in the odds of being classified as a biphilic/androphilic persister (Model 1) or a gynephilic desister (Model 2) for a 1-unit increase in the corresponding predictor, and thus $100 \times (e^B - 1)$ represents the percentage change in the odds ratio for a 1-unit increase in that predictor (115).

It can be seen from **Table 4** that only social class had a significant contribution to the prediction of group outcome at follow-up (see also **Figure 1**). The biphilic/androphilic persisters had a 13% increase in odds of coming from a lower social class background compared to the biphilic/androphilic desisters. However, social class did not predict outcome when the two desister groups were compared.

Table 3 also shows the variables of age, IQ, and social desirability scores at follow-up as a function of group. One-way ANOVAs revealed that both age and IQ differed significantly among the three groups ($ps < 0.01$), but social desirability scores did not. Duncan's multiple range test for unequal Ns showed that the gynephilic desisters were, on average, younger than both the biphilic/androphilic persisters and the biphilic/androphilic desisters (both $ps < 0.05$), who did not differ significantly from each other. Regarding IQ at follow-up, the results were similar to those for IQ in childhood. The biphilic/androphilic desisters had, on average, a higher IQ than the biphilic/androphilic persisters ($p < 0.05$) but did not differ significantly from the gynephilic desisters. There was no significant difference in IQ between the biphilic/androphilic persisters and the gynephilic desisters.

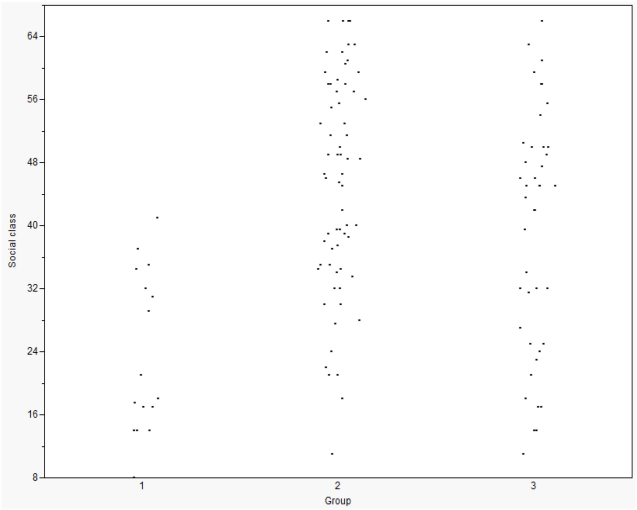

FIGURE 1 | Distribution of social class for the outcome groups at follow-up. 1 = Biphilic/androphilic persisters ($n = 16$; $M = 23.76$, $SD = 10.22$). 2 = Biphilic/androphilic desisters ($n = 66$; $M = 44.97$, $SD = 13.64$). 3 = Gynephilic desisters ($n = 42$; $M = 39.44$, $SD = 15.91$).

Childhood Sex-Typed Behavior as a Function of Gender Identity and Sexual Orientation at Follow-Up

Supplementary Table 2 shows the means or percentage scores (for dichotomous measures) of the nine sex-typed measures obtained at the assessment in childhood as a function of the three outcome groups. ANCOVAs (with age at assessment, IQ, social class, and marital status covaried) or chi-square were used to examine whether the groups differed on any of these variables.[15] There was a significant difference between the groups on four child-report measures (first drawn person on the Draw-a-Person, free play, Gender Identity Interview, and cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, and one parent-report measure (Gender Identity Questionnaire for Children). A statistical summary of these individual measures can be found in the **Supplementary Text** and the data are shown in **Supplementary Table 2**.

The childhood sex-typed behavior measures on which the groups differed were all significantly correlated (*r*s ranged from |0.30–0.76|) [reported in (77), Table 15].[16] From these six measures (first drawn person on the Draw-a-Person, free play, Gender Identity Interview, cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, cross-sex toy preference on the Playmate and Play Style Preferences Structured Interview, and the Gender Identity Questionnaire for Children), a composite score of childhood sex-typed behavior was derived for each participant by taking the average of the six variables (each expressed as *z*-scores).[17] A higher composite *z*-score indicates more cross-gender behavior at the assessment in childhood.

To evaluate the influence of childhood sex-typed behavior and demographic variables on group outcome at follow-up, a multinomial logistic regression was performed using the composite score and the demographic variables on which the groups differed–age at assessment, IQ, and social class–as predictor variables. It can be seen from **Table 5** that both social class and the composite score of childhood sex-typed behavior were significant predictors of group outcome at follow-up in the first model, which compared the biphilic/androphilic persisters to the biphilic/androphilic desisters.

The biphilic/androphilic persisters had a 274% increase in odds of having a higher composite score (i.e., more childhood cross-gender behavior) and an 11% reduction in the odds of coming from a higher social class compared to the biphilic/androphilic desisters. Age at childhood assessment and IQ did not have a significant effect on group outcome (both *p*s > 0.05). In the second model, which compared the gynephilic desisters to the biphilic/androphilic desisters, the only significant predictor of group outcome was the composite measures of sex-typed behavior. The biphilic/androphilic desisters had a 48% increase in odds of having a higher composite score compared to the gynephilic desisters.

DISCUSSION

Methodological Issues

We were not able to recruit into the study all eligible patients; however, our analyses which compared the participants vs. the non-participants did not show any substantive or pervasive differences with regard to the baseline assessment characteristics, suggesting that the internal validity of the sample was not grossly compromised (111). The majority of follow-up participants were recruited for research purposes; however, a minority entered the study after having been seen in adolescence for some clinical issue. There was some evidence that the patients who were enrolled in the study after recontacting the clinic were, on average, more extreme in their gender-variant behavior in childhood; however, the percentage who were threshold for the GID diagnosis in childhood did not differ significantly between the two subgroups. Although the percentage of persisters was higher in the subgroup that had recontacted the clinic than the subgroup recruited for research purposes only (22% vs. 9%), the difference was also not statistically significant. If anything, the direction of the difference would suggest that the overall rate of persistence may have been slightly overestimated had we relied entirely on a "research-only" follow-up sample.

Another methodological issue is that we relied on different metrics to assess gender identity and gender dysphoria at follow-up. For example, we replaced the GDIQ with the GIDYQ-AA as we viewed the latter as a better measure; in some instances,

[15]The ANCOVA model was adjusted to accommodate a categorical covariate.

[16]Although the groups did not differ significantly on cross-sex toy preference on the PPPSI, this measure is included here because there was a trend in the direction of a significant group difference.

[17]For some participants, data were not available on all six measures. In these cases, the composite score was the average of the number of variables for which there were data.

TABLE 4 | Multinomial logistic regression of group outcome at follow-up.

Predictor	Biphilic/Androphilic persisters					Gynephilic desisters				
	B	SE	Wald	*p*	e^B	*B*	SE	Wald	*p*	e^B
Age at assessment	0.11	0.14	0.62	0.433	1.12	−0.02	0.09	0.03	0.856	0.98
IQ	0.02	0.03	0.85	0.358	1.02	−0.02	0.02	1.91	0.167	0.98
Social class	−0.14	0.04	13.66	<0.001	0.87	−0.01	0.02	0.13	0.716	0.99
Marital status	0.76	0.80	0.88	0.349	0.47	−0.43	0.52	0.70	0.402	1.54

Reference group is the Biphilic/Androphilic Desisters. This group was chosen as the reference because it had the largest group size.

TABLE 5 | Multinomial logistic regression predicting group outcome at follow-up.

Predictor	Biphilic/Androphilic persisters					Gynephilic desisters				
	B	SE	Wald	*p*	e^B	*B*	SE	Wald	*p*	e^B
Age at assessment	0.26	0.16	2.90	0.09	1.30	−0.14	0.11	1.55	0.21	0.87
IQ	0.02	0.03	0.58	0.45	1.02	−0.03	0.01	2.77	0.10	0.97
Social class	−0.12	0.03	12.28	<0.001	0.89	−0.01	0.01	0.51	0.47	0.99
Composite *z*-score	1.32	0.55	5.82	0.02	3.74	−0.66	0.31	4.38	0.04	0.52

Reference group is the Biphilic/Androphilic Desisters. This group was chosen as the reference because it had the largest group size. A preliminary analysis with marital status included as a predictor variable showed that it did not have a significant effect and was, therefore, excluded in the final regression model. As suggested by Reviewer 3, per Benjamin et al. (116), for the "discovery of new effects," p-values between 0.05 and 0.005 should be viewed as "suggestive" (i.e., informative, but cautiously interpreted), and p-values < 0.005 as "significant" (i.e., stronger evidence for the implausibility of a difference merely by chance).

we relied solely on interview data or information available in the patient's medical chart. However, we did not detect any substantive difference in the percentage of persisters across these different sources of information and thus do not believe that such method variance challenges the validity of the findings.

Although a minority of participants were seen on more than one occasion for follow-up, the majority were not. Thus, our results and interpretation of the follow-up data are largely limited to one "moment in time," at a mean age of 20.58 years. It would, of course, be of value to have additional follow-up of the patients as they move further into adulthood in order to assess the stability (or lack thereof) of the data with regard to both gender identity and sexual orientation. In our own clinical experience, for example, we have observed that some of the patients seen during adolescence "fluctuated" between self-identifying as transgender and self-identifying as gay. Others have noted that a small number of apparent or presumed desisters during adolescence subsequently identified as transgender when seen at a later point in time (117).

Summary of Key Findings

The present study provided follow-up data with regard to gender identity and sexual orientation in boys referred clinically for gender dysphoria. There were three key findings: (1) the persistence of gender dysphoria was relatively low (at 12%), but obviously higher than what one would expect from base rates in the general population; (2) the percentage who had a biphilic/androphilic sexual orientation was very high (in fantasy: 65.6% after excluding those who did not report any sexual fantasies; in behavior: 63.7% after excluding those who did not have any interpersonal sexual experiences), markedly higher than what one would expect from base rates in the general population; (3) we identified some predictors (from childhood) of long-term outcome when contrasting the persisters with a biphilic/androphilic sexual orientation with the desisters with a biphilic/androphilic sexual orientation and when contrasting the desisters with a biphilic/androphilic sexual orientation and the desisters with a gynephilic sexual orientation.

The 12% persistence rate was somewhat lower than the overall persistence rate of 17.4% from the prior follow-up studies of boys combined. When compared to the three most methodologically sound follow-up studies, the persistence rate was higher than the 2.2% rate found by Green (47), but lower than the 20.3% rate found by Wallien and Cohen-Kettenis (52) and the 29.1% rate found by Steensma et al. (51). There is one methodological caveat regarding the Steensma et al. study that is worth noting. In their study, the mean interval between assessment and follow-up was relatively short (7.21 years). The patients were eligible for follow-up if they were at least 15 years of age. Given the relatively short interval between the assessment in childhood and the follow-up assessment in adolescence, this meant that patients who had been assessed at younger ages in childhood would not have been old enough to participate in the follow-up assessment. Given that Steensma et al. found that (older) age at the time of the assessment in childhood was a significant predictor of persistence, it is conceivable that their persistence rate was an overestimate. Nonetheless, in the broadest sense, our data were quite consistent with the general finding from the prior follow-up studies that desistance from gender dysphoria is by far the more common outcome.

In our study, we did not find that persistence was more common among boys who were threshold for the diagnosis of GID when compared to the boys who were subthreshold (13.6% vs. 9.8%) although the pattern was in the same direction

as that found by Wallien and Cohen-Kettenis (52) and Steensma et al. (51). We would, therefore, argue that the threshold-subthreshold distinction should not be abandoned in future follow-up studies although such studies might profit from using a symptom count of DSM indicators in addition to the dichotomous coding of the diagnosis as threshold vs. subthreshold. Consistent with both Wallien and Cohen-Kettenis and Steensma et al., our composite measure of sex-typed behavior in childhood was a significant predictor of outcome in that the patients classified as persisters with a biphilic/androphilic sexual orientation had more severe gender-variant behavior than the patients classified as desisters with a biphilic/androphilic sexual orientation; in addition, desisters with a biphilic/androphilic sexual orientation had more gender-variant behavior than the desisters with a gynephilic sexual orientation. Thus, dimensional measurement of gender identity and gender role behaviors from childhood provides added nuance in characterizing longer term trajectories with regard to both gender identity and sexual orientation.

With regard to sexual orientation at follow-up, the percentage of patients with a biphilic/androphilic sexual orientation in either fantasy or behavior was reasonably similar to those reported on in the prior follow-up studies which included standardized assessment measures (47, 51, 52). This finding also converges with three representative, general population prospective studies (118–120) and many retrospective studies (43) which document a significant association between patterns of gender-typed behavior in childhood and later sexual orientation.

The multinomial logistic regression analysis (**Table 4**) also showed a trend for the persisters with a biphilic/androphilic sexual orientation to be older at the time of the assessment in childhood compared to the desisters with a biphilic/androphilic sexual orientation; however, when the composite measure of sex-typed behavior in childhood was added to the equation (**Table 5**), age at assessment in childhood no longer showed such a trend [cf. Steensma et al. (51)]. In our smaller study of girls with GID (46), the persisters were, on average, 2.5 years older than the desisters at the time of the assessment in childhood (11.08 vs. 8.59 years) although the difference was not significant. It is our view that age at the time of a childhood assessment in relation to long-term outcome should continue to be examined in future follow-up studies.

Social class was a significant predictor of outcome: the persisters with a biphilic/androphilic sexual orientation were from a lower social class background compared to the desisters with a biphilic/androphilic sexual orientation (even after controlling for the other demographic variables). Why might this be the case? Because we had not made formal a priori predictions of outcome regarding any of our demographic variables, it is, of course, important to see whether or not it will be replicated in new follow-up studies. At present, our interpretation of the social class effect reflects on its relationship to other literatures.

One possibility pertains to the notion that acceptance of a gay or homosexual sexual identity is less in "working class" subculture (121). If this is, in fact, the case, it has been argued that transitioning from male to female—the so-called "homophobic" hypothesis with regard to gender dysphoria in adults (122)–would allow an androphilic sexual orientation to be more acceptable. Future studies would need to systematically examine whether boys with persistent GID first attempt to live as gay men before transitioning to the female gender role and whether or not this temporal sequence, when it occurs, is related to social class background.

In the present study, it could be hypothesized that the parents of persisters held less favorable views of androphilia (homosexuality) compared to the desisters and thus predisposed to persistence in order to "normalize" one's sexual orientation. However, this is simply a conjecture as parental attitudes toward homosexuality were not measured in the study sample. Indeed, none of the follow-up studies to date on boys with gender dysphoria have specifically examined attitudes toward homosexuality as a predictor of outcome.

Social class could also be a proxy for other explanatory factors. For example, in the present study, a lower social class background was significantly correlated with age at assessment in childhood ($r = 0.44$) and families where there had been a separation/divorce, etc. ($r = 0.58$). If one wanted to make the case that a later age at assessment might be associated with persistence (for a variety of reasons), perhaps social class is associated with a "delay" in seeking out an assessment and possible treatment (e.g., family stress, various other mental health challenges in the child and/or the family, etc.). In one study comparing the demographic characteristics of children vs. adolescents clinic-referred for gender dysphoria, it was found that the adolescents were more likely than the children to come from a lower social class background and from families in which there had been a separation/divorce, etc. (123).

Clinical Implications

What clinical implications might be drawn from our data on the persistence and desistence rates of gender dysphoria in children? First, it should be recognized that the boys in the current study were seen during a period of time when treatment recommendations, if such were made, often aimed to reduce the gender dysphoria between the child's felt gender identity and biological sex. If one peruses the treatment literature, such recommendations were carried out using many therapeutic modalities: psychotherapy or psychoanalysis, behavior therapy, group therapy, parent-counseling, and interventions in the naturalistic environment, such as encouragement of same-sex peer relations [see, e.g., (124–126); for reviews, see (127, 128)].[18]

[18]This "broad stroke" summary of therapeutic goals is not meant to minimize the complexity of ethical issues regarding how treatment has been conceptualized over the years [see, e.g., (129–133)]. In the early years, treatment recommendations included other goals: for example, Bakwin (44) wrote that "Suggestions for management…[were]…designed to encourage gender appropriate behavior *and* to prevent homosexuality" [p. 620, emphasis added; see also (134)]. Rekers (135) was subsequently quite transparent regarding the influence of his own religious beliefs in formulating treatment goals, sometimes congruent with parents' religious beliefs (see p. 131). Prayer appears to have guided Rekers' selection of behavior therapy as a treatment modality for the treatment of his patients with childhood GID (p. 131). Money and Russo (50) wondered what the course of psychosexual differentiation might be if "a group of boys with discordance of gender identity/role [were] transferred from the home of origin to, say, a children's recovery center or foster home…as happens in the case of child-abuse dwarfism…" (p. 40). In our own clinic, although some parents might have desired or requested that treatment be designed in order to prevent homosexuality, this was a goal that we never endorsed [see (136), pp. 391–393]. Over the years, many secular-minded

In our own sample, the kinds of treatments that the boys received, if any, were quite variable but it is beyond the scope of this article to describe them in general [however, for examples, see (136, 140, 141)]. It can, however, be said with certainty that the vast majority of boys were seen during a particular period of time when the therapeutic approach of recommending or supporting a gender social transition prior to puberty was not made. Indeed, in the current study, there was only one patient who had socially transitioned prior to puberty (at the suggestion and support of the professionals involved in this individual's care) and this particular patient was one of the persisters with a biphilic/androphilic sexual orientation. Second, it should also be recognized that, for the boys seen in the current study, none who were in late childhood and had (likely) entered puberty (Tanner Stage 2) had received puberty-blocking hormone treatment (GnRH analogs) to suppress somatic masculinization (142, 143) until sometime during adolescence.

In contrast, in recent years, it has become more common for some clinicians to recommend a gender social transition prior to puberty [e.g., (69, 144–147); for discussion, see (148–150)]. It has also become more common for parents to have already implemented a gender social transition on their own, without any formal input from a health professional (151). As argued by Zucker (64, 152), this is a very different type of psychosocial treatment designed to reduce gender dysphoria when compared to the other kinds of treatments noted above that have been recommended over the years.

The study by Steensma et al. (51), which found the highest rate of persistence, included some patients who had made a partial or complete gender social transition prior to puberty and this variable proved to be a unique predictor of persistence (see the Introduction). Rae et al. (153) recruited from a variety of community groups a sample of 85 markedly gender non-conforming children (Mean age, 7.5 years), none of whom had socially transitioned at a baseline assessment. At the time of follow-up, at a mean of 2.1 years later, 36 (42.3%) had socially transitioned and 49 (57.6%) had not. Using a composite of various metrics of gender identity and gender role behaviors, Rae et al. found that those who subsequently socially transitioned had more extreme gender-variant behavior at baseline than those who had not. Thus, this short-term follow-up study was consistent with the longer-term findings reported on by Wallien and Cohen-Kettenis (52), Steensma et al. (51), and the present study.

To date, however, there are no long-term follow-up studies of clinic-referred samples of children who had all socially transitioned prior to puberty. Future follow-up studies should be able to capture a much larger subgroup of such children and compared to those who have not with regard to long-term outcome with regard to persistence and desistance [e.g., (154)]. The persistence-desistance rates found in this study and the ones preceding it can be used as a comparative benchmark for samples in which a social transition took place prior to puberty.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The research protocol was reviewed and approved by Clarke Institute of Psychiatry (subsequently the Centre for Addiction and Mental Health) and the University of Toronto. All participants who completed the face-to-face assessment gave written informed consent.

AUTHOR CONTRIBUTIONS

DS contributed to the conceptualization, data collection, data analysis, interpretation, and writing of the paper. SB contributed to the conceptualization and interpretation of the study. KZ contributed to the conceptualization, data collection, data analysis, interpretation, and writing of the paper. All authors contributed to the article and approved the submitted version.

FUNDING

DS was supported by an Ontario Graduate Scholarship (2008–2009, 2009–2010, 2010–2011) and the Social Sciences Humanities Research Council (2010–2011). Funding for this study was provided, in part, by the Laidlaw Foundation and internal research funds from the Clarke Institute of Psychiatry.

ACKNOWLEDGMENTS

This article is based on DS's doctoral dissertation at the University of Toronto. Preliminary versions of this article were presented at the 1989 meeting of the Society for Research in Child and Adolescent Psychopathology, Miami Beach, Florida and the 2010 Gender Development Research Conference, San Francisco, California.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.632784/full#supplementary-material

clinicians–although clearly opposed to any type of preventive efforts with regard to sexual orientation–argued in favor of reducing gender dysphoria vis-à-vis natal sex, if that was feasible. Meyer-Bahlburg (125), for example, wrote: "…we cannot rule out the possibility that early successful treatment of childhood GID will diminish the role of a continuation of GID into adulthood. If so, successful treatment would also reduce the need for the long and difficult process of sex reassignment which includes hormonal and surgical procedures with substantial medical risks and complications" (p. 362). Along similar lines, Cohen-Kettenis and Pfäfflin (33) remarked: "Relatively little dispute exists regarding the prevention of transsexualism, though evidence about the effectiveness of treatment in preventing adult transsexualism is also virtually nonexistent" (p. 120). In more recent years, what the best-practice should be for the treatment of gender dysphoria in children has been widely discussed and debated, which highlight the various limitations of treatment effectiveness studies (137–139).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RB declared a past co-authorship with one of the authors KZ to the handling Editor.

ACADÉMIE NATIONALE DE MÉDECINE

FONDÉE LE 20 DÉCEMBRE 1820

Medicine and gender transidentity in children and adolescents

Press release of the French National Academy of Medicine[1]

February 25, 2022

Gender transidentity is the strong sense, for more than 6 months, of identification with a gender different from that assigned at birth. This feeling can cause a significant and prolonged suffering, which can lead to a risk of suicide (a). No genetic predisposition has been found.

The recognition of this disharmony is not new, but a very strong increase in the demand for physicians for this reason has been observed (1, 2) in North America, then in the countries of northern Europe and, more recently, in France, particularly in children and adolescents. For example, a recent study within a dozen high schools in Pittsburgh revealed a prevalence that was much higher than previously estimated in the United States (3): 10% of students declared themselves to be transgender or non-binary or of uncertain gender (b). In 2003, the Royal Children's Hospital in Melbourne had diagnosed gender dysphoria in only one child, while today it treats nearly 200.

Whatever the mechanisms involved in the adolescent – overuse of social networks, greater social acceptability, or example in the entourage - this epidemic-like phenomenon results in the appearance of cases or even clusters in the immediate surroundings (4). This primarily social problem is based, in part, on a questioning of an excessively dichotomous vision of gender identity by some young people.

The medical demand is accompanied by an increasing supply of care, in the form of consultations or treatment in specialized clinics, because of the distress it causes rather than a mental illness per se. Many medical specialties in the field of pediatrics are concerned. First of all psychiatry, then, if the transidentity appears real or if the malaise persists, endocrinology gynecology and finally surgery are concerned.

However, a great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause. In this respect, it is important to recall the recent decision (May 2021) of the Karolinska University Hospital in Stockholm to ban the use of hormone blockers.

Although, in France, the use of hormone blockers or hormones of the opposite sex is possible with parental authorization at any age, the greatest reserve is required in their use, given the

[1] This Press release, adopted by the French Academy of Medicine on February 25, 2022, by 59 votes for, 20 against and 13 abstentions, was approved, in its revised version, by the Board of Directors on February 28, 2022.

side effects such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause.

As for surgical treatments, in particular mastectomy, which is authorized in France from the age of 14, and those involving the external genitalia (vulva, penis), their irreversible nature must be emphasized.

Therefore, faced with a request for care for this reason, it is essential to provide, first of all, a medical and psychological support to these children or adolescents, but also to their parents, especially since there is no test to distinguish a "structural" gender dysphoria from transient dysphoria in adolescence. Moreover, the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to "detransition". It is therefore advisable to extend as much as possible the psychological support phase.

The National academy of medicine draws the attention of the medical community to the increasing demand for care in the context of gender transidentity in children and adolescents and recommends:

- A psychological support as long as possible for children and adolescents expressing a desire to transition and their parents;

- In the event of a persistent desire for transition, a careful decision about medical treatment with hormone blockers or hormones of the opposite sex within the framework of Multi-disciplinary Consultation Meetings;

- The introduction of an appropriate clinical training in medical studies to inform and guide young people and their families;

- The promotion of clinical and biological as well as ethical research, which is still too rare in France on this subject.

- The vigilance of parents in response to their children's questions on transidentity or their malaise, underlining the addictive character of excessive consultation of social networks which is both harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence.

Glossary:

a. Gender dysphoria is the medical term used to describe the distress resulting from the incongruence between the felt gender and the gender assigned at birth (5).

b. A non-binary person is a person whose gender identity is neither male nor female.

c. A transgender person adopts the appearance and lifestyle of a sex different from that assigned at birth. Whether born male or female, the transgender persons changes, or even rejects, their original gender identity. The sex registered on his or her civil status does not correspond to the appearance he or she sends back. This does not necessarily lead to a therapeutic approach.

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Received: 20 January 2023 | Revised: 5 April 2023 | Accepted: 17 April 2023

DOI: 10.1111/apa.16791

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

A systematic review of hormone treatment for children with gender dysphoria and recommendations for research

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Funding information
Swedish Agency for Health Technology Assessment and Assessment of Social Services

Abstract

Aim: The aim of this systematic review was to assess the effects on psychosocial and mental health, cognition, body composition, and metabolic markers of hormone treatment in children with gender dysphoria.

Methods: Systematic review essentially follows PRISMA. We searched PubMed, EMBASE and thirteen other databases until 9 November 2021 for English-language studies of hormone therapy in children with gender dysphoria. Of 9934 potential studies identified with abstracts reviewed, 195 were assessed in full text, and 24 were relevant.

Results: In 21 studies, adolescents were given gonadotropin-releasing hormone analogues (GnRHa) treatment. In three studies, cross-sex hormone treatment (CSHT) was given without previous GnRHa treatment. No randomised controlled trials were identified. The few longitudinal observational studies were hampered by small numbers and high attrition rates. Hence, the long-term effects of hormone therapy on psychosocial health could not be evaluated. Concerning bone health, GnRHa treatment delays bone maturation and bone mineral density gain, which, however, was found to partially recover during CSHT when studied at age 22 years.

Abbreviations: BMD, bone mineral density; CSHT, cross-sex hormone treatment; DXA, dual-energy X-ray absorptiometry; GnRHa, gonadotropin-releasing hormone agonist (analogues); GRADE, grades of recommendation, assessment, development and evaluation; ICD, International Classification of Diseases; MRI, magnetic resonance imaging; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services.

Berit Kriström and Mikael Landén have equal contrbution.

[†]Part of the original study group but deceased in December 2021.

Conclusion: Evidence to assess the effects of hormone treatment on the above fields in children with gender dysphoria is insufficient. To improve future research, we present the GENDHOR checklist, a checklist for studies in gender dysphoria.

KEYWORDS
adolescent, bone density, gender dysphoria, gonadotropin-releasing hormone agonist, psychosocial functioning

1 | INTRODUCTION

Gender incongruence refers to a mismatch between the biological sex and perceived gender identity. When gender incongruence causes significant discomfort, it is called gender dysphoria. When gender dysphoria causes clinically significant distress, the condition might meet the diagnostic criteria for transsexualism according to the (international classification of disease) ICD-10 guidelines,[1] or gender dysphoria according to the DSM-5.[2] Gender identity-affirming health care is provided to ease gender dysphoria.[3] The treatment aims to align bodily characteristics with the individual's gender identity, and usually includes cross-sex hormone treatment (CSHT), as well as chest and genital surgery.

In youth with gender dysphoria, gonadotropin-releasing hormone analogues (GnRHa) have been used to inhibit spontaneous puberty development. The rationale is to prevent irreversible bodily changes and give young individuals time to explore their gender identity. Following the first case report in which a GnRHa was used to suppress puberty in a female-to-male transsexual individual,[4] the '"Dutch protocol" was developed.[5] According to this protocol, young pubertal people presenting with gender dysphoria should first undergo a thorough psychological evaluation. If the diagnosis gender dysphoria is confirmed, GnRHa treatment is recommended to start during the early stages of puberty (Tanner stages 2–3). If gender dysphoria subsides, the individual may discontinue GnRHa treatment, at which point spontaneous puberty will restart. If gender dysphoria persists, CSHT might start at age 16 years and sex-reassignment surgery at 18 years. Gender dysphoria in youth was a rare phenomenon when the Dutch multidisciplinary protocol for the treatment of gender dysphoria was introduced. Seeking care for gender dysphoria has since become increasingly common in younger people in many parts of the western world,[6,7] with an exponential rise among children born female.[8] Although not all children with gender dysphoria receive gender identity affirming treatment, there has been an ensuing increase in hormones to treat children with gender dysphoria, of which data on the effects and side effects are limited. There is no previous systematic review or meta-analysis of hormone treatment for children with gender dysphoria.

This systematic review aimed at assessing (a) psychosocial effects, (b) effects on bone health, (c) effects on body composition and metabolism, and (d) satisfaction and therapy persistence in children aged <18 years with gender dysphoria undergoing hormone therapy.

Key Notes

- This systematic review assessed psychosocial effects, bone health, body composition and metabolism, and therapy persistence in children (<18 years of age) with gender dysphoria undergoing treatment with gonadotropin-releasing hormone analogues (GnRHa).
- Long-term effects of hormone therapy on psychosocial health are unknown. GnRHa treatment delays bone maturation and gain in bone mineral density.
- GnRHa treatment in children with gender dysphoria should be considered experimental treatment of individual cases rather than standard procedure.

In this review, trans women are referred to as male-to-female and trans men as female-to-male.

2 | METHODS

2.1 | Preregistration

This systematic review originated from a 2-year commissioned work from the governmental body the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). Ongoing SBU reviews are registered on the SBU website (https://www.sbu.se/en/ongoing-projects/) but not recorded in external databases.

2.2 | Selection criteria

The search was restricted to children aged <18 years with reported gender dysphoria. We included observational studies, randomised controlled trials, and systematic reviews according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] Case reports, editorials, and non-human studies were excluded from further review. The search was limited to English-language publications.

2.3 | Search strategy

Two professional information specialists at the Swedish Agency for Health Technology Assessment and Assessment for Social Services (SBU) performed a comprehensive search of the following medical databases up until 9 November 2021: CINAHL (EBSCO), Cochrane Library (Wiley), EMBASE (Embase.com), PsycINFO (EBSCO), PubMed (NLM), Scopus (Elsevier), and SocINDEX (EBSCO). They also searched the Campbell Library, Epistemonikos, Evidence Search, International HTA database, as well as three NIHR Centre for Reviews and Dissemination (CRD) databases: Database of Abstracts of Reviews of Effects (DARE), Health, and Technology Assessment (HTA), and NHS Economic Evaluation Database (EED). Finally, we searched PROSPERO, an international prospective register for systematic reviews, to identify any relevant ongoing systematic reviews but found none. The search, selection, and assessment were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] The search and selection processes are outlined in Figure 1. Only studies of low or moderate bias were eligible for this review. Full literature search strategy is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-1-litteratursokning.pdf).

2.4 | Relevance, risk of bias, and quality of evidence

Two independent experts checked all hits for relevance. Relevant studies (based on a pre-defined PICO) were then evaluated for risk of bias, also by two independent experts, according to ROBINS-I (Risk of bias in non-randomised studies of interventions).[10,11] Robins-I assesses possible bias in seven domains: confounding; bias due to selection, measurement classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

If the two reviewers did not agree on content or quality, the paper was discussed in the larger research team of four experts (JFL, PR, BK, ML). Randomised controlled trials were planned to be assessed by RoB−2.[10,11] To rate the quality of evidence for specific outcomes, we used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.[12] GRADE has four levels of evidence (very low, low, moderate, high) and considers five domains that can decrease the level of certainty one or two levels (risk of bias, imprecision, inconsistency, indirectness (similar to 'external validity'), and publication bias).

2.5 | Data extraction

Two reviewers (MH, JA) retrieved data from the included studies. The data extracted included the outcomes mental and psychosocial health including suicidality, anthropometric measures and metabolism, bone health, adverse events, and the characteristics of each study including age at referral or intake, age at start of GnRHa treatment, age at start of CSHT, number of participants enrolled in study, number of transgender participants, number of hormone treated transgender participants, number of non-transgender participants, number of participants evaluated, treatment type (drugs, dosages, type of administration, treatment frequency), total treatment duration, and total follow-up time. The full data extraction of included studies is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-3-tabellverk-over-inkluderade-studier.pdf).

2.6 | Statistics

No statistical analyses were performed.

2.7 | Ethics

Ethical approval is not applicable for this systematic review.

3 | RESULTS

3.1 | Identified studies

After duplicate removal, the search yielded 9934 potential studies (Figure 1). Of these, 195 were selected for thorough reading. Of these, 36 were relevant and assessed for risk of bias. Twelve studies were excluded because of high risk for bias, leaving 24 studies with low to moderate, moderate, or moderate to high risk of bias reviewed in this paper. A list of excluded studies is provided at the SBU web page (https://www.sbu.se/contentassets/4062b596a35c4e1383405766b7365076/bilaga-2-exkluderade-studier-med-hog-risk-for-bias.pdf).

3.2 | Characteristics of the 24 studies

All 24 relevant studies had been published since 2014 (Table 1). Study participant age at the start of GnRHa therapy was typically between 11 and 15 years (range 9–18.6 years), with CSHT rarely being introduced before age 15. Except for the Hisle-Gorman et al.[6] ($n=3754$ participants) and Mullins et al.[13] ($n=611$) papers, few studies included >200 individuals. GnRHa treatment often continued for around 2 years, sometimes up to 4 years, and similar treatment durations were observed or reported for CSHT as observations were usually not reported after age 18 years. Full details of included studies are given at the SBU web page. Overall, there were eight studies on GnRH alone, 13 studies on GnRH + CSHT, and three studies on CSHT alone.

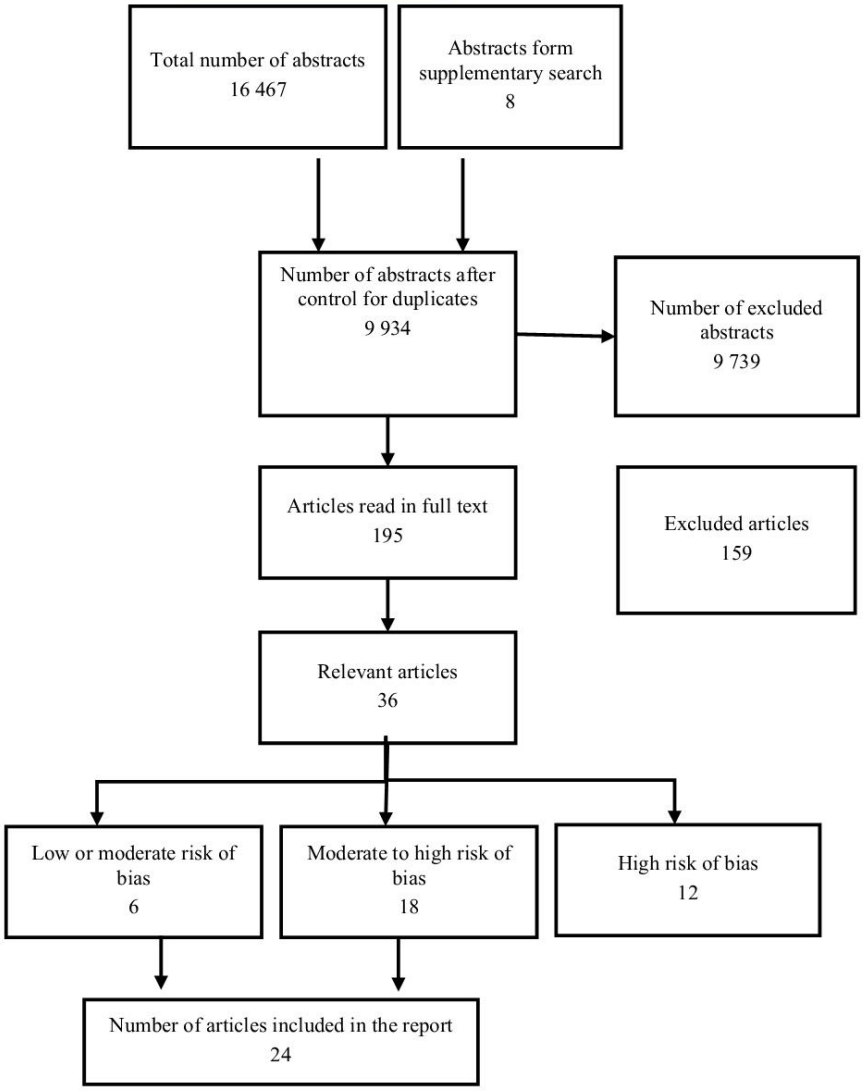

FIGURE 1 PRISMA flow diagram.

3.3 | Psychosocial and mental health

Table 2 outlines the six studies that examined psychosocial outcomes and cognitive effects.[14–19] Three of these studies found significantly improved overall psychosocial function after GnRHa treatment as measured by the Children's Global Assessment Scale (CGAS).[14–16] Two of these studies observed no statistically significant change in gender dysphoria.[15,16] Two of these studies reported significantly improved self-rated quality of life after treatment measured through Kidscreen-27, Short Form-8 (SF-8), Child Behaviour Checklist (CBCL) (parent report), and Youth Self Report (YSR),[16,17] while another study reported no statistically significant differences in anxiety and depression between those who started and not started hormone therapy.[18]

Because these studies were hampered by small number of participants and substantial risk of selection bias, the long-term effects of hormone treatment on psychosocial health could not be evaluated. Of note, the above studies do not allow separation of potential effects of psychological intervention independent of hormonal effects.

3.4 | Cognitive outcomes

We could only identify one study of low-moderate bias on cognitive outcomes in children with gender dysphoria receiving GnRHa therapy.[19] This cross-sectional study from the USA comprised 20 treated (8 male-to-female and 12 female-to-male) and 20 untreated (10 male-to-female and 10 female-to-male) young transgender persons and a control group ($n = 45$). Controls were identified from age-matched family members and friends. The Tower of London task was administered to assess executive functioning. The study neither found differences in cognitive function between treated and untreated transgender persons, nor between treated transgender persons and controls. However, because no before-after GnRHa therapy analyses were performed, the study

TABLE 1 Overview of 24 included studies.

Reference	Ages of patients (years)			Numbers of patients						Interventions			Time: duration and follow-up			Outcomes extracted
	Age at intake range (mean)	Age at start of GnRH range (mean)	Age at start of CSHT range (mean)	*n* referred	*n* TG enrolled	*n* TG HT	*n* TG non-HT	*n* non-TG	*n* TG HT at last FU	GnRH	CSHT	Surgery[b]	GnRH duration range (mean)	CSHT duration range (mean)	Follow-Up time range (mean)	Mental health Bone health Anthropometrics Metabolism
Mental health																
de Vries 2014[14]	11–17 (13.6)	11.5–18.5 (14.8)	13.9–19 (16.7)	196	111	55			32	x	x	x	1 year[a]	4 years[a]		UGDS, global functioning (CGAS), depression (BDI), anxiety (STAI), anger (TPI)
Costa 2015[15]	12–17 (15.5)	13–17 (16.5)		436	201	101	100		35	x			1 year		1.5 years	UGDS, psychosocial functioning (CGAS)
Becker-Hebly 2020[17]		11–17 (15.5)	13–17 (15.5)	434	75	54	21		54	x	x	x	0.5–4 years[a]	0.5–4 years[a]	7–49 months	Global functioning (CGAS), psychosocial functioning (YSR/ASR)
Cantu 2020[18]		11–xx (15)	xx–18 (15)		80	42	38		28	x	x		NR	NR	1–11 months (5 months)	Psychosocial functioning (PHQ-9, GAD-7), acute distress, suicidality
Carmichael 2021[16]		12.0–15.3 (13.6)			44	44			14	x			12–59 months (31 months)		12–36 months	UGDS, CGAS, psychological functioning (CBCL, YSR), Self-harm, BIS, HRQoL (Kidscreen52)
Hisle-Gorman 2021[6]	8–13 (10)		16.6–19.8 (18.2)		3754	963		6603	963	x	x		0.7–2.7 years (1.5)	0.7–2.7 years (1.5)	8.5 years	Mental health diagnosis, psychotropic medication use, medication days, service use
Staphorsius 2015[19]		min 12			41	20	20	45		x			0.6–2.6 years (1.6)			Psychological functioning (CBCL), cognitive function (executive function task)

Reference	Ages of patients (years)			Numbers of patients						Interventions			Time: duration and follow-up			Outcomes extracted
	Age at intake range (mean)	Age at start of GnRH range (mean)	Age at start of CSHT range (mean)	*n* referred	*n* TG enrolled	*n* TG HT	*n* TG non-HT	*n* non-TG	*n* TG HT at last FU	GnRH	CSHT	Surgery[b]	GnRH duration range (mean)	CSHT duration range (mean)	Follow-Up time range (mean)	Mental health Bone health Anthropometrics Metabolism
Bone health																
Joseph 2019[23]		12–14 (13)				70			70	x			1–xx years		up to 2.8 years	Height, weight, BMI BMD, BMAD, Z-score (hip, spine)
Klink 2015[21]		11.4–18.3 (15)	15.6–19 (16)			34			34	x	x	x	0.25–8 years	xx–8 years	up to age 22	Height, BMD, aBMD, Z-score, T-score (femoral neck, lumbar spine)
Vlot 2017[22]		11.5–18.6 (14)	14.0–19.5 (16)		215	70			57	x	x		1–xx years		up to 2 years	Height, BMAD, Z-score (hip, lumbar spine), bone markers (P1NP, OC, ICTP)
Schagen 2020[20]		12.2–16.5 (14)	15.0–17.9 (16)			127			121	x	x		1.5–4 years	3 years		aBMD, Z-score (hip)
Stoffers 2019[24]		11.8–18.0 (16)	14.9–18.4 (17.2)		64	62			15	x	x		3 months–3 years	5 months–3 years	2 years	Height, BP, BMD, Z-score (femoral neck, lumbar spine)
Navabi 2021[25]		13.4–17.4 (15)			198	172			116	x			6 months–2 years		1.5 years	BMD, aBMAD, Z-score (hip, lumbar spine)
van der Loos 2021[26]		11–17	15–17			322			322	x	x	x	1–3 years	2–6 years	up to 4 years	Subperiostal width, endocortical diameter
Lee 2020[27]		9.6–13.4 (11.5)			95	63			63	x			2 months			BMD, aBMAD, Z-score (hip, lumbar spine)
Anthropometrics and metabolism																
Schagen 2016[28]		11.1–18.6 (14)			138	116			77	x			3–12 months		1 year	Height, weight, BMI, lean body mass, liver enzymes, creatinine
Klaver 2018[31]		12.7–17.3[a] (15)	15.3–17.8[a] (16)	489	192	192			192	x	x	x	0.5–2.9 years (1.5[a])	1.6–3.4 years (2.9[a])	age 22	Weight, BMI, total body %, WHR

Reference	Ages of patients (years)			Numbers of patients						Interventions			Time: duration and follow-up			Outcomes extracted
	Age at intake range (mean)	Age at start of GnRH range (mean)	Age at start of CSHT range (mean)	*n* referred	*n* TG enrolled	*n* TG HT	*n* TG non-HT	*n* non-TG	*n* TG HT at last FU	GnRH	CSHT	Surgery[b]	GnRH duration range (mean)	CSHT duration range (mean)	Follow-Up time range (mean)	Mental health Bone health Anthropometrics Metabolism
Klaver 2020[32]		12.8–17.2[a] (14.9)	15.3–17.8[a] (16.6)		192	192			192	x	x	x	0.5–2.9 years (1.5)[a]	1.1–3.4 years (2.5[a])	age 22	BMI, SBP, DBP, glucose, insulin, HOMA-IR, cholesterol, triglycerides
Perl 2020[33]		13.4–15.4 (14)	14.2–16.0 (15)		48	15			15	x	x		2–4 months	2–6 months		BMI, BP
Schulmeister 2021[29]		9.0–14.5 (11.5)			92	55	226		55	x			10–14 months		1 year	Height velocity, BMI, z-score
Nokoff 2021[30]		10.2–14.1 (12)			17	17	31		17	x			0.5–5.8 years			Insulin, glucose HbA1c, HOMA-IR, body fat, % lean mass
Tack 2016[34]			NR (15–17)		45	43			43		x			6–18 months (12)	1.5 years	Height, weight, BMI, triglycerides, cholesterol, suicide, side effects
Jarin 2017[35]		103–xx	xx–25 (16–18)		116	116			116	(x)	x				2 years	BMI, BP, haematocrit, Hb, cholesterol
Mullins 2021[13]			13–24 (17)	1406	611	611			611		x			0.8–2.8 years (1.5 years)	3 years	Haematology, thrombosis, BMI

Note: Number of patients:*n* referred = number of patients referred to gender clinic for evaluation of gender dysphoria (not same at number of patients receiving GD diagnosis)*n* TG enrolled = number of patients enrolled in the study at start*n* TG = number of patients with gender dysphori*an* TG HT = number of patients with gender dysphoria treated with hormones (GnRH alone, GnRH + CSHT, or CSHT only)*n* TG non-HT = number of patients with gender dysphoria treated NOT with hormones*n* TG HT at last FU = number of patients with gender dysphoria treated with hormones (GnRH alone, GnRH + CSHT, or CSHT only) evaluated at last follow-up time*n* non-TG = number of subjects in study without gender dysphoria (reference population).

Abbreviations: BDI, Beck Depression Inventory; BIS, Body Image Scale; BMAD, Bone Mineral Apparent Density; BMD, Bone Mineral Density; BMI, Body Mass Index; BP, Blood pressure; CBCL, Child Behaviour Checklist; CGAS, Global functioning Children's Global Assessment Scale, [higher scores (>80) indicating better global functioning]; CSHT, Cross-Sex Hormone Treatment/ gender-affirming treatment, testosterone, oestradiol, cyproterone acetate (CA), spironolactone, lynestrenol; GAD-7, Generalised Anxiety Disorder-7; GnRH, Gonadotropin Releasing Hormone analogue: triptorelin; HRQoL, Health Related Quality of Life; HT Hormone treatment, either GnRH, CSHT, or both; PHQ-9, Patient Health Questionnaire-9; SF-8, Short Form-8: (<18 years); STAI, Spielberger's Trait Anxiety; TG, Transgender; TPI, Anger Spielberger's Trait Anger; UGDS, Utrecht Gender Dysphoria Scale, score range 12–60 points [high score = high level of GD]; WHR, Waist-hip ratio; YSR, Youth Self Report: YSR (ages 11–18 years); Adult version (ASR, >18 years), [higher scores reflect higher degree of problems]; NR, not reported.

[a]Calculated by SBU.

[b]Surgery = any kind of gender reassignment surgery (gonadectomy, mastectomy, hysterectomy, laryngeal surgery, hair removal, phalloplasty, vaginoplasty).

TABLE 2 Summary of findings on psychosocial outcomes of puberty-blocking treatment (GnRHa) treatment in children with gender dysphoria.[14–19]

Outcome measures	Number of study participants, description of studies	Main result	"Certainty of evidence"	Deduction in GRADE[a]
Global function	*n* on hormones = 254 *n* evaluated = 113 Four observational cohort studies: one prospective and three retrospective studies[14–17]	Improved global function as assessed with the CGAS	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]
Suicide ideation	*n* on hormones = 42 *n* evaluated = 28 One prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment)[18]	No change in suicide ideation	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]
Gender dysphoria	*n* on hormones = 145 *n* evaluated = 49 Two prospective observational cohort studies[15,16]	No change in gender dysphoria	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]
Depression	*n* on hormones = 97 *n* evaluated = 60 Two prospective observational cohort studies of which one included mixed treatment[14,18]	No change in depression	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]
Anxiety	n on hormones = 97 n evaluated = 60 Two prospective observational cohort studies[14,18]	No change in anxiety	Cannot be assessed	−2 risk of overall bias[a] −2 precision[b]
Cognition	*n* on hormones = 20 *n* evaluated = 20 One study[19]	No change in cognition compared with matched controls	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]
Quality of life	*n* on hormones = 98 *n* evaluated = 46 Two observational cohort studies, whereof one retrospective[16,17]	1. Improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by gender-affirming hormone treatment[17] 2. Some improvement[16]	Cannot be assessed	−2 risk of overall bias[b] −2 precision[c]

Abbreviation: CGAS, Children's Global Assessment Scale.

[a]Starting at 4 for optimal studies in each study type.

[b]Selection of study participants is difficult to assess, analysis not based on stage in puberty development.

[c]Few study subjects in each study, heterogeneity in outcome and analyses.

could not investigate potential cognitive effects of hormone therapy.

3.5 | Bone health outcomes

Six longitudinal studies used dual-energy X-ray absorptiometry (DXA) scan technology to explore bone health before and again after some time with GnRHa treatment (Table 3). The second DXA scan usually coincided with CSHT initiation leading to different follow-up durations. The third DXA scan was performed after variable time with CSHT, performed with variable dosing and administration. The lumbar spine and hip were most often examined. One study investigated bone geometry.[20] Six studies were retrospective[21–26] and one study was prospective.[20] An additional study was cross-sectional where study participants in early puberty (Tanner stages 2–3) were examined only once, before the start of GnRHa therapy.[27]

Three studies reported a lower bone mineral density (BMD) in patients before or at start of GnRHa treatment compared with the general population of the same biological sex and age.[21,23,27] During GnRHa treatment, BMD estimated through area or volume, and expressed in z-scores increased less compared with general population reference values. However, the mean absolute BMD remained unchanged up to 2–3 years of GnRHa treatment.[20,23] The initiation of CSHT stimulated bone maturation and mineral accrual, increasing BMD.[21,22] After a median CSHT duration of 5.4 years in in female-to-male and 5.8 years in male-to-female, the lumbar spine mean areal BMD z-score was still significantly lower than at the start of GnRH therapy, while the other volume BMD and femoral neck estimates had normalised.[21] In another study, female-to-male receiving testosterone replacement therapy for 1–2 years had not regained their group mean BMD z-score registered at the start of GnRHa therapy.[24]

Bone geometry, estimated as subperiosteal width and endocortical diameter, was studied on DXA scans before start of GnRHa