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Position Statement

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Genetic testing and screening in children

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ABSTRACT

Genetic testing has progressed rapidly over the past two decades and is becoming common in paediatrics. This statement provides an overview of recent developments that may impact genetic testing in children. Genetics is a rapidly evolving field, and this statement focuses specifically on expanded newborn screening, next generation sequencing (NGS), incidental findings, direct-to-consumer testing, histocompatibility testing, and genetic testing in a research context.

Keywords: Genetic screening; Genetic testing; Paediatrics.

The first karyotype (chromosomal snapshot) was generated in the 1950s, and resolution has been improving ever since. The Canadian Paediatric Society (CPS) released its first statement guiding genetic testing in healthy children in 2003 (1), posted an addendum in 2008, and comparable statements on the ethical and policy issues of genetic testing and screening in children have been published by other health organizations more recently (2–4). Genomic chromosomal microarrays were introduced in routine genetic clinical practice by the 2000s, which has improved resolution compared with standard karyotypes significantly. At the same time, sequencing technologies have greatly improved. Whole exome sequencing (WES) is increasingly used on a clinical basis for children with heterogeneous medical presentations, with superior diagnostic yield compared with previously available molecular and cytogenetic testing. By providing improved diagnostic rates, WES has allowed for more targeted medical management for complex cases (5).

PREDICTIVE GENETIC TESTING FOR ACTIONABLE CONDITIONS

It is appropriate clinical practice for a treating paediatrician to offer genetic testing to confirm a medical diagnosis in a symptomatic infant, child, or youth, usually by referral to clinical genetics. Genetic testing may also be conducted for a healthy child with a positive family history of a genetic condition, particularly if early treatment may affect morbidity or mortality. More specifically, testing is used when genetic conditions are penetrant in the paediatric period and there is good evidence that medical intervention before symptom onset will improve outcome. One such example is multiple endocrine neoplasia type 2 (MEN2), an autosomal dominant condition associated with high risk for cancer and for which close follow-up and prophylactic thyroidectomy are recommended (6). Also, knowing a child's genetic risk can significantly reduce invasive procedures.

For conditions that are actionable in childhood, predictive testing should be offered to children at increased risk, based on their family history. Predictive testing for disorders not actionable until adulthood is typically not recommended for minors, though this distinction has been challenged in the literature based on the best interests of families (7). A further distinction is that when a condition is not actionable until adulthood, best practice should protect the child's right to an open future. That is, respecting a young person's present and future autonomy may include deferring the decision to test until a child or youth is fully informed and able to participate in the consent process.

THE DIFFERENCE BETWEEN "CARRIER" AND "PREDICTIVE" TESTING FOR LESS PENETRANT DISORDERS

Regarding terminology (8), the word "carrier" has been used historically to refer to an individual of either sex who possesses a single pathogenic variant for an autosomal recessive condition

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(e.g., cystic fibrosis) *or* to a female who possesses a single pathogenic variant for an X-linked recessive condition. Defined either way, a carrier is not at risk for developing clinical manifestations of a heritable condition, but is at risk for having an affected child.

More recently, "carrier" has been used to refer to individuals who harbour a single variant for an autosomal dominant condition with incomplete penetrance, i.e., where they are at risk for manifesting the disease. To complicate terminology further, some females with a single variant for an X-linked condition can also manifest symptoms, though they are often milder than in males. In this document, carriers are individuals who are *not* at risk for developing the disease.

When a single variant may be sufficient to cause symptoms, genetic testing for it in individuals who are currently symptom-free is considered "predictive" testing.

THE DILEMMA POSED BY INCIDENTAL FINDINGS

Incidental findings are unrelated to the initial indication for testing. Historically, genetic testing was hypothesis-driven, meaning that clinicians made a working diagnosis and tested specifically for this condition only. As testing for larger panels of genes has become feasible and, potentially, more advantageous, the likelihood of incidentally exposing a variant for a condition for which clinical suspicion was low or absent is significant.

The Canadian College of Medical Geneticists (CCMG) recommends an approach to testing that (as much as possible) "filters out" genes that are not related to a young person's clinical presentation. For incidentally discovered pathogenic variants discovered despite using this approach, they also recommend that only findings actionable in the paediatric period be reported to families (9).

The American College of Medical Genetics (ACMG) created a list of genes that they deemed to be actionable in 2013, which was updated in 2017 and in 2021. The most recent version (10) includes 73 genes, and laboratories may use this list to look to screen secondary findings. Some laboratories use lists developed in-house. When families choose to test only for genes that are actionable in the paediatric period, information about variants in genes associated with adult-onset conditions is not reported. Such information is also not made available to the child's clinician, the child at a later date, or to parents, unless a re-analysis of the entire WES or whole genome sequencing (WGS) data is requested. When parents are given the option of searching for secondary findings in children, they should be provided with in-depth counselling and a referral to a specialized clinic or services.

CONSENT, PARENTAL PERMISSION, AND SUBSTITUTE DECISION-MAKING

A person's rights to autonomy and self-determination underpin the principle of informed consent. Consent to a medical procedure must be informed, voluntary (secured without coercion), and the consenting individual must be capable of giving it. Young children are not fully capable of consent as described, so genetic testing is performed with permission from parents (11) or a substitute decision maker (SDM) with the child's best interests being paramount. Parental permission is predicated on the assumption that parents have their child's best interests at heart and strive to protect them.

Being appropriately and thoroughly informed is essential to medical decision-making, and the benefits and risks of genetic testing must be carefully considered, discussed, and weighed. Both the right of the child *not* to know test findings and the right to know them when old enough to understand and act on this knowledge must be protected. One possible exception to this rule is when the benefits of knowing test results sooner than later outweigh the benefits of future self-determination. These are difficult situations, and practitioners may need to consider a parent's desire to know whether a child has inherited a disease-causing gene against the child's need to know, at present or later on. Typically, a decision should be deferred until the child is able to make it.

CONSENT IS TIED TO DEVELOPMENTAL CAPACITY

The ability to provide consent is, in part, developmentally determined (12). Children may be able to agree with or assent to testing, while adolescents may be capable of fully understanding the nature of a genetic condition and the consequences of agreeing to, or refusing, medical management (11,13), providing they are fully informed. A person's ability to apprehend and appreciate potential social risks of their condition, such as loss of privacy, stigmatization, and discriminatory employment or insurance practices (14), may require even more maturity.

PARENTAL REQUESTS FOR GENETIC TESTING

Parents and health care providers (HCPs) who request genetic testing should understand its ethical and social implications. When parents are determined to test a healthy child, despite being fully informed of ethical and social concerns, the HCP must weigh the benefits of testing against potential harms. HCPs should not feel obligated to facilitate testing when they do not believe it is in the child's best interests. Parents cannot mandate medical interventions or tests that may not be in their child's best interest, including genetic testing (15). Exceptional cases exist, however, such as when *not* testing may cause more harm than testing, and may require assistance from a medical ethicist or legal counsel.

SOCIAL RISKS

Genetic information is considered uniquely private because, both historically and currently, stigmatization and discrimination have been real social concerns for individuals and groups whose health status may be at risk or compromised by a genetic condition (16). In Canada, Bill S-201, The Genetic Non-Discrimination Act, passed in 2017, prevents employers and insurance companies from accessing genetic testing results or requesting an individual to undergo genetic testing (17).

An individual's right to decide about testing and control of genetic information can be complicated by larger family obligations and responsibilities. However, gene testing for a child that

is imposed is never acceptable, even when results might be of benefit to other family members (18).

PSYCHOLOGICAL CONCERNS

The psychological impacts of knowing whether a gene conferring risk has (or has not) been inherited are well considered in the literature (19). Studies of adults at risk for Huntington's disease have shown that a positive result in a well-prepared individual may not be devastating. However, receiving a negative result (i.e., where the individual is not at increased risk) has also been found to increase psychological stress in some cases (19). Family dynamics can be affected by testing. For example, parents may feel profoundly guilty or responsible, and concerns about parents being over-protective of their genetically at-risk child have also been raised.

Testing healthy individuals for carrier status for X-linked or autosomal recessive conditions is generally considered to be minimally risky compared with testing those who are at risk for adult-onset disorders (20). However, the knowledge of being a carrier for a genetic condition that could affect offspring can have negative effects. One study of women tested for fragile X carrier status demonstrated that 5 months after testing, carriers were found to have situational specific changes in feelings about themselves, predominantly due to concerns about implications (21).

REPRODUCTIVE PRIVACY

Although carrier testing to inform future reproductive decision-making might be perceived as low risk because the carrier will not manifest the condition, the child's right to future reproductive privacy is an important consideration. Wide variability in the uptake of carrier testing by adults of reproductive age makes it difficult to judge whether testing children to inform reproductive decisions years later is actually in their best interests. In one ethical exploration of carrier testing of children for Tay Sachs disease, Dena Davis explains (22): "Children will grow up to be adults. Respecting them as potential adults means respecting their right and ability when they reach that state, to have autonomy over information personal to them." When an infant or child is tested for carrier status, they are deprived of their right to autonomy over information personal to them as soon as results are shared with parents or family members. In one study of fragile X carriers, the average age that parents thought their daughters should be tested for the condition was 10 years, which was significantly younger than the age they felt knowing their own genetic status was appropriate (15 years) (23).

NEWBORN SCREENING

While all provinces and territories in Canada have implemented newborn screening, there is no national testing guideline. Because most infant screening tests are for actionable genetic disorders, their results can significantly affect the lives of children and families. Saskatchewan, for example, requires screening for congenital hypothyroidism and phenylketonuria by law. Newborn screening is generally regarded as a standard of neonatal care, although parents have the option of refusal. Some jurisdictions screen extensively, and the number of conditions being screened for is likely to increase.

Some authorities have proposed that newborn screening could be performed by whole exome or whole genome sequencing, but because abnormal metabolites are still better detected with current targeted screening strategies, the genetic approach has not been widely adopted (24,25). Current newborn screens can detect carriers (for cystic fibrosis and hemoglobinopathies, for example), but the manifest benefits of screening early far outweigh the risks of testing, which is recommended for all infants. In Ontario, report on carrier status for hemoglobinopathies must be specifically requested, and families are referred to a hematology clinic before proceeding. Advice on tests for other conditions can be obtained from individual screening programs.

CHROMOSOMAL MICROARRAY AND FRAGILE X TESTING IN CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD)

Chromosomal microarray and fragile X testing are commonly recommended when evaluating children with developmental delay with or without ASD (26). Chromosomal microarray may detect pathogenic or likely pathogenic microdeletions or microduplications. A variation of unclear clinical significance occurs when there is insufficient information to interpret a particular finding with confidence at the present time. Fragile X syndrome is caused by a trinucleotide expansion of CGG repeats in the *FMR1* gene (27). Both severity and type of clinical manifestations depend on the individual's sex and the number of CGG repeats.

HISTOCOMPATIBILITY TESTING

Histocompatibility testing in infants or children to select for bone marrow or organ donation for a close family member is considered permissible (2), provided that a multidisciplinary team including a bioethicist, an advocate for the child, and social work is involved. This policy is based on achieving the greatest overall benefit for the family as a whole.

DIRECT-TO-CONSUMER (DTC) TESTING

Genetic tests such as 23andMe, marketed directly to consumers (styled DTC-genetic testing or DTC-GT), are now available in Canada. Such companies have different disclaimers regarding the minimum age for providing samples. For example, 23andMe specifies that a child must be 13 years old. However, because most companies use "spit kits," there is no mechanism to ensure the person contributing the sample actually is the person identified on the application form or to verify their minimum age.

DTC-GT companies in Canadian vary widely. Three subtypes of (potentially) medically relevant DTC are offered: (1) assessment of risk for common multifactorial diseases (e.g., diabetes); (2) targeted variant analysis for single gene disorders; and (3) sequencing. Some families also use these tests for ancestry tracing. Many significant genetic risk and protective factors for multifactorial conditions have not yet been identified, which can lead to divergent risk interpretations among

companies even when they have tested samples from the same individual. For targeted variant analysis and sequencing, the test may not include all clinically relevant genes or variants and yield falsely reassuring results. Moreover, testing typically includes adult-onset conditions and carrier status even when paediatric samples are tested. Genetic changes that are only weakly associated with disease may be reported, leading to anxiety, inappropriate additional testing or, potentially, social discrimination.

When making medical decisions based on results from genetic testing, the test itself should meet all the recommendations made by the CCMG in 2012. Not all DTC-GT meet these standards. For the multiple reasons described here, the risks of DTC-GT far outweigh benefits, and these companies are ill-equipped to protect the best interests of children. Therefore, using DTC-GT for children is not recommended.

ADOPTION

The necessity of protecting the best interests of children applies equally to candidates for adoption. Adoption agencies are obligated to seek and disclose children's medical histories, including genetic information, to prospective adoptive families. However, they are not obligated to request genetic testing of biological families or children who are candidates for adoption. Nor should they be, because a positive finding could decrease the chance of adoption significantly and affect the child negatively in other ways.

A definitive joint statement from the ACMG and American Society of Human Genetics recommended in 2000 that timely medical benefit should be the guiding principle of genetic testing for children. Prospective adoptees should not be tested "for the purpose of detecting genetic variations of, or predisposition to physical, mental, or behavioral traits within the normal range" as part of the adoption process (28). Adopted children can and should benefit from appropriate diagnostic testing when presenting symptomatically.

RESEARCH TESTING

When parents, children, or youth are appropriately informed and capable of medical decision-making, they should also be made aware of potential difficulties when interpreting gene testing results, especially in research settings (29). Before testing, it should always be clear how research results will be distributed, and to whom (30). Some laboratories providing results have a primary research focus and may not hold to the same quality assessment and control standards as clinical laboratories. The reliability and validity of interpreting test results, for gene abnormalities specifically, should be thoroughly discussed with all recipients of such information. Involving a qualified geneticist or genetic counsellor can help families and HCPs to interpret results and, when needful, to differentiate between clinical practice testing and (perhaps less certain) research results (29). Research findings should be validated in a clinical laboratory or assessed for quality and clinical relevance by an independent review before being used for clinical decision-making (30).

RECOMMENDATIONS

1. Whenever genetic testing for children is being considered, health care providers (HCPs) and/or qualified specialists must fully inform parents—and children and youth when they are capable—of any psychological and social risks. Open discussion regarding familial risk, conducted in an age-appropriate manner, is encouraged for the whole family, with the best interests of children always paramount. Involving genetic counsellors and/or medical genetics in such discussions is strongly recommended.
2. Evidence for timely medical benefit of genetic testing for a child's condition should guide medical decision-making. Specifically, genetic testing to confirm a diagnosis in a symptomatic child is appropriate. When clinically indicated by family history, genetic testing for conditions actionable within the paediatric period is also appropriate, even in an asymptomatic child.
3. For genetic conditions that typically do not present until adulthood, susceptibility or predictive testing should be deferred until a child is capable of deciding whether to test.
4. Testing children for carrier status to inform reproductive decision-making later in life is discouraged. Requests for genetic testing for this purpose by competent, well-informed adolescents should be considered and accompanied by appropriate counselling. The decision to include the family in decision-making should be made by the adolescent and the care team.
5. When parents request genetic testing for their healthy child or youth with no evidence of medical or other benefit to the person concerned, HCPs are not obliged to comply. They should clearly explain the reasons for not acceding to a request for testing, and document discussion(s). In cases where not testing a child might arguably entail greater risk than testing, a request for a consultation to medical genetics or to an ethicist is recommended.
6. Except in clear cases of timely medical benefit, infants and children being considered for adoption should only undergo genetic testing comparable to screens and diagnostic tests offered to children in the general population.
7. Physicians, with assistance from a genetic counsellor or specialist, should inform parents (and children or youth capable of involvement) concerning the limitations of research results, which can vary with the understanding of the gene disorder and by testing modality. Recipients of genetic information should be cautioned against acting on research results for clinical decision-making.
8. Use of direct-to-consumer genetic testing in children is strongly discouraged because its risks far outweigh benefits for this age group.

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