Medical Genetics

Twelve Things Physicians and Patients Should Question
by
Canadian College of Medical Geneticists
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Choosing Wisely Canada™
In collaboration with the Canadian Medical Association

1 Don't use non-invasive prenatal detection of fetal aneuploidies by cell-free DNA as a diagnostic test.

Non-invasive prenatal detection of fetal aneuploidies by cell-free DNA, also called non-invasive prenatal testing (NIPT) and non-invasive prenatal screening (NIPS), is a method of non-invasive fetal DNA testing done through a maternal blood sample. NIPT testing for common aneuploidies, microdeletions and sex chromosome disorders is clinically available to patients in Canada. NIPT is a highly sensitive and specific screening test, but is not diagnostic. Even in high-risk populations, there can be false positive NIPT results. Genetic counselling, along with confirmatory testing via amniocentesis or chorionic villus sampling, should be done prior to using the result to impact management of a pregnancy.

2 Don't make medical decisions based on results of direct to consumer genetic testing (DTC-GT) without a clear understanding of the limitations and validity of the test.

Three types of potentially medically-relevant DTC-GT are available: (1) assessment of risk for common multifactorial diseases (e.g., diabetes, etc.); (2) targeted mutation analysis for single gene disorders; and, (3) sequencing. Some DTC-GT companies state that they do not guarantee the accuracy or reliability of their tests. Many of the significant genetic risk and protective factors for multifactorial conditions have not been identified. This leads to greatly divergent risk interpretations between companies, even when performed on the same individual. For targeted mutation analysis and sequencing, the specific test may not include all clinically relevant genes or mutations; resulting in false reassurance. Genetic changes that are only weakly associated with disease may be reported, leading to anxiety or inappropriate additional testing. When making medical decisions based on results of genetic testing, the test should meet the recommendations made by the Canadian College of Medical Geneticists in 2012. Not all DTC-GT meet these recommendations.

3 Don't order a chromosome analysis by doing a karyotype for individuals with intellectual disability/developmental delay of unknown etiology.

Microarray is the first line test for individuals with intellectual disability/developmental delay without a recognizable syndrome. Indeed, a microarray has a much higher detection rate (15 - 20%) compared to a karyotype (3 - 4%) in individuals presenting for this clinical indication. A karyotype remains important in limited clinical situations where a specific numerical or structural chromosomal syndrome, such as Down syndrome, is suspected.

4 Don't order whole exome sequencing prior to genetic counselling.

Whole exome sequencing (WES) is a powerful test for individuals suspected of having an underlying genetic diagnosis. However, WES increases the likelihood of unexpected findings, which may or may not be clinically significant. Further, due to methodological limitations, WES may not always be the correct test to order as WES will not detect all genetic causes of disease (for example, it will not detect chromosomal structural differences). Both informative and uninformative results can lead to complex patient and family psychosocial repercussions, and could impair future insurability. Genetic counselling facilitates informed decision-making. Given complexity of results, WES should only be ordered after counselling by a qualified health care provider.

5 Don't order carrier testing in children.

Carrier testing is primarily useful in the reproductive period to determine the risk of an individual having a child affected by the condition for which testing is being considered. Knowing that a child is a carrier of an X-linked or autosomal recessive condition usually does not alter medical care in the pediatric years since most carriers are unaffected. Thus, in most situations, there is not a medical indication for carrier testing in a child. Undertaking carrier testing of a child violates the right of the child to make his or her own decision about testing and could potentially impair future insurability. An exception could be made for a mature adolescent who may be able to understand the reproductive implications of carrier testing after appropriate genetic counselling.

6 Don't order rapid or expedited testing if the results will not change management.

Rapid genomic tests are increasingly available both pre- and postnatally and can decrease time to diagnosis compared to standard tests. Yet, there is often an added cost to their use and their utility and cost-effectiveness are not entirely

established. Before pursuing testing in an expedited timeframe, gathering a patient's values and preferences is crucial, particularly as it relates to potential decision points in a pregnancy. While genetic information may be valued at an earlier stage in a disease course and rapid results may be preferred by patients, balancing the potential increased cost against conventional genetic turnaround times is particularly important when results are not expected to have immediate management implications.

7 Don't order broad panel or genomic testing when targeted testing is more appropriate due to specificity of the phenotype.

When there is a specific condition suspected based on clinical features or where clinical criteria are available, targeted testing is more appropriate than broad panel or genomic testing. The advantages of targeted testing are that the gene(s) or chromosomal region(s) being tested are well known to be associated with specific risks, often have management guidelines available if a pathogenic variant is found, and it is simpler to convey the specific limitations and benefits of doing targeted testing. The analytic validity, clinical validity and clinical utility are important domains in genetic testing evaluation and are easier to determine for a targeted test rather than for a broad or genomic test where the phenotype may not be anticipated, or the gene may be of moderate or low risk. Broad panel or genomic tests increase anxiety with increased number of variants of uncertain significance (VUS), increase the risk of misinterpretation or misattribution to less well understood gene or genomic region, and lead to increased costs of unnecessary screening and surgeries.

8 Don't order a genome-based test when another genetic testing method is more appropriate.

Genome-wide diagnostic testing, including whole exome sequencing and microarray analysis, has become widely used as a first-line test for patients with a variety of clinical presentations. While these broad tests can provide a good diagnostic yield, they also have technical limitations and are unable to reliably diagnose some specific genetic conditions, including spinal muscular atrophy (SMA), congenital adrenal hyperplasia (CAH), Facioscapulohumeral Muscular Dystrophy (FSHD), imprinting disorders (Beckwith-Wiedemann syndrome, Prader-Willi syndrome, Angelman syndrome, Russel-Silver syndrome, etc.), and repeat expansion disorders (Fragile X syndrome and related disorders, Huntington disease, Myotonic Dystrophy, Friedreich's ataxia, Spinocerebellar ataxia, etc.), among others. The mechanism underlying the condition must be considered to determine whether a test can rule out or rule in a diagnosis; if a disorder is being considered as part of the differential diagnosis and cannot reliably be detected by genome-based testing, then a disease- or gene-specific molecular diagnostic test is required. When an incorrect test is ordered, it may give a false sense of reassurance if a negative result is returned, and it could delay diagnosis for the patient. In addition, this is potentially a poor use of resources.

9 Don't routinely offer carrier screening when the chance of having an affected pregnancy is low.

Assessment of an increased risk of inherited disease should be available to all individuals considering a pregnancy. Genetic counselling for possible carrier screening should be offered to individuals identified as being at elevated risk of transmission of an inherited condition based on family history, ethnic background, or past medical/obstetrical history. When the a priori risk is elevated, carrier testing may be offered. Expanded carrier testing using large panels yields few carrier pairs (at most 1% even with larger panels) and therefore is not recommended as a routine test at this time. Additionally, the utilization of limited laboratory, clinical and genetic counselling resources requires stewardship. Since the evidence is limited, routine carrier screening of all individuals is not recommended at this time. However, this may be revisited if evidence of effectiveness and efficiency is established and implementation strategies are proposed.

10 Don't order a sequencing test after a negative exome study.

Whole exome sequencing (WES) is a next generation sequencing method that includes the protein-coding sequence of the genome. WES covers >99% of sequence variants, and several studies have demonstrated that >98% of relevant sequence variants identified on targeted panels were identified on WES. Most clinical laboratories use the same sequencing methods for WES and gene panels. Thus, the additional diagnostic yield of panel sequencing after WES is likely to be low.

11 Don't automatically order metabolic testing for a child with isolated global developmental delay/intellectual disability.

Intellectual developmental disorders (IDD) affect 2.5% of the population. Inherited metabolic disorders (IMD's) may present with IDD and often other neurologic or systemic features and some IMD's are treatable. Despite years of implementing a biochemical testing algorithm on a research basis in one province, the yield of testing was not increased for IMD's.
There are significant harms associated with over-investigation. Although the cost of biochemical testing is inexpensive compared to molecular or specialized tests, it is still a significant burden on the health care system. The cost of the tests is not the only consideration, since significant human resources are required for pre-test counselling, coordination of sample collection, transport and analysis, interpretation of results and follow-up. Even more importantly, there may be harm to children and families subjected to further blood draws and urine tests, extending the diagnostic odyssey as repeat testing is often required for a positive or uncertain result. There is extensive literature on the harms of false positives from newborn screening, but this is balanced against the yield of testing for treatable IMD's on the newborn screen and efficacy of early intervention. Similar data of the benefits of screening all children with IDD for IMD's does not exist. There are well-recognized red flags suggestive of an IMD in children with IDD and it would be appropriate to do targeted metabolic testing in those situations (so called "intellectual disability plus"). Consideration should also be given to patients who did not have newborn screening (NBS) for IMD. Further biochemical testing may also be a valuable tool when molecular testing is negative or

uncertain, to provide functional evidence of pathogenicity.

12 **Don’t proceed with genetic testing too early in a patient’s presentation.**

Watchful waiting refers to a policy of taking no immediate action with respect to a situation or course of events but of following its development intently. Different areas in medicine employ watchful waiting and have found it not to impact patient outcome in select situations. Given the increased availability, genetic testing is often requested early in a patient’s presentation. However, genetic conditions and our ability to understand and diagnose them frequently evolve over time. Early investigation may result in increased cost due to repeated application of non-targeted testing, with concomitant increased likelihood of detecting variants of uncertain significance, as well as poorer result interpretation for reports reliant on complete phenotyping. When the phenotype is incomplete or unclear, and there are no red flags, such as deteriorating patient status, potential for change in management, or information necessary for timely reproductive counseling, watchful waiting may be appropriate.

How the list was created

Recommendations 1-5

The medical genetics Choosing Wisely Canada recommendations were generated by the Ethics, Education and Public Policy (E2P2) committee of the Canadian College of Medical Geneticists (CCMG) in consultation with the entire membership of the CCMG. In the summer of 2015, the E2P2 committee generated a first list of potential statements and a pilot survey was distributed during the CCMG annual conference in September 2015. Based on the feedback received, the E2P2 committee modified the statements and generated new ones. An electronic survey (via Survey Monkey) was distributed to the entire CCMG membership in March 2016; members were asked to rank their 5 favourite statements. The answers were weighted and the 5 top statements were selected. Members of the E2P2 committee reviewed the literature and generated a rationale for each of the 5 statements. The 5 statements and their rationale were orally presented during the general assembly of the CCMG annual meeting in June 2016. Comments received at that time led to a slight revision of the wording of the rationale of some statements by the members of the E2P2 committee. The statements and their rationale were then posted online for comments in the members-only section of the CCMG website for one month during the summer of 2016. Members of the CCMG all received an email prompting them to review these statements. The E2P2 committee reviewed all comments received and slightly altered the wording of some statements. The list was then circulated to all medical professional society leads engaged in Choosing Wisely Canada for review. Comments received were considered by the E2P2 committee and the list was finalized.

Recommendations 6-12

The additional recommendations were generated by the Ethics, Education and Public Policy (E2P2) committee of the Canadian College of Medical Geneticists (CCMG) in consultation with the entire membership of the CCMG. A list of potential statements was drafted in the fall and winter of 2019 and then distributed to CCMG membership to review and complete an electronic survey. The survey was completed in spring 2020 and analyzed by the E2P2 committee leading to modifications of some of the statements. Members of the E2P2 committee reviewed the literature and generated rationales for the statements. The statements were then reviewed by the board of directors for the CCMG. They were submitted to Choosing Wisely Canada for review. The list of recommendations 6-12 were circulated to all medical professional society leads engaged in Choosing Wisely Canada for review. Comments received were considered by the E2P2 committee and the list was finalized.

Sources

1. Benn P, et al. Ethical and practical challenges in providing noninvasive prenatal testing for chromosome abnormalities: an update. Curr Opin Obstet Gynecol. 2016 Apr;28(2):119-24. PMID: 26938150.
Mersy E, et al. Noninvasive detection of fetal trisomy 21: systematic review and report of quality and outcomes of diagnostic accuracy studies performed between 1997 and 2012. Hum Reprod Update. 2013 Jul-Aug;19(4):318-29. PMID: 23396607.

2. Canadian College of Medical Geneticists. Direct-To-Consumer (DTC) Genetic Testing in This Country [Internet]. 2015 Jul 19 [cited 2017 Jan 3].
CCMG Ethics and Public Policy Committee, Nelson TN, Armstrong L, et al. CCMG statement on direct-to-consumer genetic testing. Clin Genet. 2012 Jan;81(1):1-3. PMID: 21943145.
Caulfield T, et al. Direct-to-consumer genetic testing - where should we focus the policy debate? Med J Aust. 2013 May 20;198(9):499-500. PMID: 23682895.
Peikoff, K. I Had My DNA Picture Taken, With Varying Results, New York Times [Internet]. 2013 Dec 30 [cited 2017 Jan 3].

3. Michelson DJ, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2011 Oct 25;77(17):1629-35. PMID: 21956720.
Moeschler JB, et al. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014 Sep;134(3):e903-18. PMID: 25157020.
Newman WG, et al. Array comparative genomic hybridization for diagnosis of developmental delay: an exploratory cost-consequences analysis. Clin Genet. 2007 Mar;71(3):254-9. PMID: 17309648.

4. Boycott K, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. J Med Genet. 2015 Jul;52(7):431-7. PMID: 25951830.
Krabbenborg L, et al. Understanding the Psychosocial Effects of WES Test Results on Parents of Children with Rare Diseases. J Genet Couns. 2016 Dec;25(6):1207-1214. PMID: 27098417.
Sawyer SL, et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clin Genet. 2016 Mar;89(3):275-84. PMID: 26283276.

5. Borry P, et al. Carrier testing in minors: a systematic review of guidelines and position papers. Eur J Hum Genet. 2006 Feb;14(2):133-8. PMID: 16267502.
Committee on Bioethics, American College of Medical Genetics, et al. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013 Mar;131(3):620-2. PMID: 23428972.
Guidelines for genetic testing of healthy children. Paediatr Child Health. 2003 Jan;8(1):42-52. PMID: 20011555.

6. Meng L, et al. Use of exome sequencing for infants in intensive care units: ascertainment of severe single-gene disorders and effect on medical management. JAMA Pediatr. 2017 Dec 4;171(12):e173438. PMID: 28973083.
Petrikin JE, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. NPJ Genomic Med. 2018;Feb 9;3:6. PMID: 29449963.
Stoll K, et al. Supporting Patient Autonomy and Informed Decision-Making in Prenatal Genetic Testing. Cold Spring Harb Perspect Med. 2020 Jun 1;10(6):a036509. doi: 10.1101/cshperspect.a036509. PMID: 31615869.
Young C, et al. Rapid Genome-wide Testing: A Review of Clinical Utility, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Sep 20. PMID: 31721549.

7. Adams VA, et al. Insights and Considerations for Large Panel Genetic Tests. Informed DNA. 2019 Oct 22.
Lynce F, et al. How far do we go with genetic evaluation? Gene, Panel, and Tumour Testing. Am Soc Clin Oncol Educ Book. 2016; 35:e72-e78. PMID: 27249773.
National Academies of Sciences, Engineering, and Medicine et al. An Evidence Framework for Genetic Testing. Washington (DC): National Academies Press (US); 2017 Mar 27. PMID: 28418631.

8. Nimkarn S, et al. 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia. GeneReviews® [Internet]. 2002 Feb 26. PMID: 20301350.
Preston MK, et al. Facioscapulohumeral Muscular Dystrophy. GeneReviews® [Internet]. 1999 Mar 8.

Prior TW, et al. Spinal Muscular Atrophy. GeneReviews® [Internet]. 2000 Feb 24.
Wallace SE, et al. Resources for Genetics Professionals — Genetic Disorders Caused by Imprinting Errors and Uniparental Disomy Not Detectable by Sequence Analysis. GeneReviews® [Internet]. 2017 Mar 14.
Wallace SE, et al. Resources for Genetics Professionals — Genetic Disorders Caused by Nucleotide Repeat Expansions and Contractions. 2017 Mar 14 GeneReviews® [Internet].

9 Hussein N, et al. Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease. Cochrane Database Syst Rev. 2021 Oct 11;10(10):CD010849. PMID: 34634131.
Peyser A, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med. 2019 Jun;21(6):1400-1406. PMID: 30327537.
Wilson RD, et al. Joint SOGC-CCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing. J Obstet Gynaecol Can. 2016 Aug;38(8):742-762.e3. PMID: 27638987.

10 Dunn P, et al. Next Generation Sequencing Methods for Diagnosis of Epilepsy Syndromes. Front. Genet. 2018 Feb 7;9:20. PMID: 29467791.
Kong SW, et al. Measuring coverage and accuracy of whole-exome sequencing in clinical context. Genetics in Medicine. 2018 Dec;20(12):1617-1626. PMID: 29789557.
LaDuca H, et al. Exome sequencing covers >98% of mutations identified on targeted next generation sequencing panels. PLoS One. 2017; 12(2): e0170843. PMID: 28152038.
Sun Y, et al. Next-generation diagnostics: gene panel, exome, or whole genome? Hum Mutat. 2015 Jun;36(6):648-55. PMID: 25772376.

11 Carmichael N, et al. "Is it going to hurt?": the impact of the diagnostic odyssey on children and their families. J Genet Couns. 2015 Apr;24(2):325-35. PMID: 25277096.
Gross SD, et al. From public health emergency to public health service: the implications of evolving criteria for newborn screening panels. Pediatrics. 2006 Mar;117(3):923-9. PMID: 16510675.
Kwon C, et al. The Magnitude and Challenge of False-Positive Newborn Screening Test Results. Arch Pediatr Adolesc Med. 2000;154(7):714-718. PMID: 10891024.
Richards S. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. PMID: 25741868.
Sayson B, et al. Retrospective analysis supports algorithm as efficient diagnostic approach to treatable intellectual developmental disabilities. Mol Genet Metab. 2015 May;115(1):1-9. PMID: 25801009.
Vallance, et al. Diagnostic yield from routine metabolic screening tests in evaluation of global developmental delay and intellectual disability. Paediatr Child Health. 2020 Dec 19;26(6):344-348. PMID: 34676012.

12 Allanson, et al. J Craniofac Genet Dev Biol. Time and natural history: the changing face. 1989;9(1):21-8. PMID: 2793999.
Baynam, et al. Phenotyping: targeting genotype's rich cousin for diagnosis. J Paediatr Child Health. 2015 Apr;51(4):381-6. PMID: 25109851.
Galia, et al. Whole body magnetic resonance in indolent lymphomas under watchful waiting: The time is now. Eur Radio. 2018 Mar;28(3):1187-1193. PMID: 29018927.
Lieberthal, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013 Mar;131(3):e964-99. PMID: 23439909.
Reistrup, et al. Watchful waiting vs repair for asymptomatic or minimally symptomatic inguinal hernia in men: a systematic review. Hernia. 2021 Oct;25(5):1121-1128. PMID: 32910297.
Rittenmeyer, et al. The experience of adults who choose watchful waiting or active surveillance as an approach to medical treatment: a qualitative systematic review. JBI Database System Rev Implement 2016 Feb;14(2):174-255. PMID: 27536798.
Vissers et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. Genet Med. 2017 Sep;19(9):1055-1063. PMID: 28333917.

About the Canadian College of Medical Geneticists

Medical genetics is the branch of medicine concerned with the effect of genetic variation on human development and health and also with the study, diagnosis, management, and prevention of genetic and related disorders in individuals, families, and communities. The Canadian College of Medical Geneticists is the national specialty society that represents genetic specialists (MDs and PhDs) who see patients with genetic conditions and/or direct laboratories that perform diagnostic testing for genetic conditions.

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About Choosing Wisely Canada

Choosing Wisely Canada is the national voice for reducing unnecessary tests and treatments in health care. One of its important functions is to help clinicians and patients engage in conversations that lead to smart and effective care choices.

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