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1. Don't order rapid or expedited genetic testing if the results will not change management.
2. Don't use broad panel or genomic testing when the phenotype is specific and targeted testing would be more appropriate.
3. Don't assume that genome-based testing will detect all genetic diagnoses.
4. Don't routinely offer carrier screening when the chance of having an affected pregnancy is low.
5. Don't order a sequencing test after a negative exome study.
6. Don't automatically order metabolic testing on every child with global developmental delay/intellectual disability.
7. Don't discount the value of watchful waiting.

1. 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.[1,2] Yet, there is often (but not always) an added cost to their use and their utility and cost-effectiveness are not entirely established.[3] 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.[4] While genetic information may be valued at an earlier stage in a disease course, balancing the potential increased cost against conventional genetic turnaround times is particularly important in a publicly funded healthcare system when results are not expected to have immediate management implications.

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2. Don't use 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, and the condition is known to be caused by a single gene, a small number of genes or a chromosomal cause, 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.[1] The analytic validity, clinical validity and clinical utility are important domains in genetic testing evaluation[2] 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.[1] With a broad panel or genomic test, there may be fewer individuals who have been found to have variants in lower diagnostic yield genes, thereby increasing the risk of uncertain classifications.[1] In addition to anxiety caused by variants of uncertain significance (VUS), there can be misinterpretation in the clinical utility of a VUS or a pathogenic variant in a less well understood gene or genomic region, leading to increased costs of unnecessary screening and surgeries.[3]

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3. Don't assume that genome-based testing will detect all genetic diagnoses.

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),[1] congenital adrenal hyperplasia (CAH),[2] Facioscapulohumeral Muscular Dystrophy (FSHD),[3] imprinting disorders (Beckwith-Wiedemann syndrome, Prader-Willi syndrome, Angelman syndrome, Russel-Silver syndrome, etc.),[4] and repeat expansion disorders (Fragile X syndrome and related disorders, Huntington disease, Myotonic Dystrophy, Friedreich's ataxia, Spinocerebellar ataxia, etc.),[5] 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.

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4. 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.[1] When the *a priori* risk is elevated, carrier testing may be offered. However, routine carrier screening of all individuals is not recommended at this time, even for common autosomal recessive conditions such as cystic fibrosis or spinal muscular atrophy (SMA), or X-linked conditions such as Fragile X syndrome, as there is a lack of evidence of effectiveness for universal carrier screening at this time.[2] Additionally, laboratory infrastructures as well as clinical and counselling resources are not universally available across Canada.[1]

Expanded carrier testing is now possible thanks to genomic technologies using large panels, but such tests are currently only available to Canadians through private laboratories at this time.[1] The identification of two carriers (i.e. both individuals are carriers of the same condition) with such panels remains rare (at most 1% even with larger panels).[3] Because such testing yields few carrier pairs and requires private pay, in the absence of identifiable increased risk, routinely offering expanded carrier screening is not recommended at this time. If an individual requests such testing, these considerations should be balanced with the individual's particular context and discussed in genetic counselling.

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5. 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,[1] and several studies have demonstrated that >98% of relevant sequence variants identified on targeted panels were identified on WES.[2,3,4] Thus, the additional diagnostic yield of panel sequencing after WES is likely to be low. However, if there is a strong clinical suspicion of a particular diagnosis or group of genes, most reporting laboratories can be contacted to reassess WES data in this context; this can be particularly useful if new phenotypic data becomes available. Similarly, exome reanalysis is offered by most commercial laboratories 1-2 years after the initial result, and has been noted to have an increased diagnostic yield of 10-15% in a number of studies.[1,5,6] If a condition is suspected and there are concerns about a particular gene of interest not being sufficiently covered, further testing could be considered in consultation with a clinical geneticist.

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6. Don't automatically order metabolic testing on every child with global developmental delay/intellectual disability.

Intellectual developmental disorders (IDD) affect 2.5% of the population.[1] Inherited metabolic disorders (IMD's) may present with IDD and often other neurologic or systemic features and some IMD's are treatable. The Canadian Pediatric Society (CPS) recently published a statement recommending metabolic testing in all children with IDD as part of the first tier of investigations.[2] However, despite years of implementing a similar algorithm on a research basis in one province, the yield of testing was not increased for IMD's.[3]

There are significant harms associated with over-investigation. Although the cost of biochemical testing recommended for tier 1 investigation is inexpensive compared to molecular or specialized tests, it is still a significant burden on the health care system.[2] 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.[4,5] 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.[6] 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").[2] Further biochemical testing may also be a valuable tool when molecular testing is negative or uncertain, to provide functional evidence of pathogenicity.[7]

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7. Don't discount the value of watchful waiting.

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.[1] Different areas in medicine employ watchful waiting and have found it not to impact patient outcome in select situations.[2,3,4] 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.[5] Early investigation may result in increased cost due to repeated application of non-targeted testing,[6] with concomitant increased likelihood of detecting variants of uncertain significance, as well as poorer result interpretation for reports reliant on complete phenotyping.[7] 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.

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