Genetics Education Canada - Knowledge Organization
Centre d'éducation en génétique canadien - Connaissances organisées

Untangling the Helix 2015: Genomics for primary care providers

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2015 Family Medicine Forum

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Enclosed:

- **Hereditary Breast and Ovarian Cancer (HBOC) syndrome** Point of Care Tool: Part I of this tool is used to predict which individuals should be referred for genetic counselling due to increased risk for a hereditary breast cancer syndrome including but not limited to HBOC syndrome caused by mutations in *BRCA1* and *BRCA2* genes. Part II of this tool is used to identify individuals who are at high risk to carry a mutation in *BRCA1* or *BRCA2* genes.

- Four GEC-KO *on the run* resources. These are concise summaries for healthcare providers on a genetic disorder, technology or topic written by an expert with input from a genetic counsellor, geneticist and family physician. They are evidence-based and referenced, and feature a 'Bottom line' with recommendations.
    a) **Direct-to-Consumer genetic testing**
    b) **Noninvasive Prenatal Testing (NIPT)**
    c) **Prenatal Chromosomal microarray**
    d) **Consanguinity**

All handouts (*except HBOC*), presentation slide sets and more are available on www.geneticseducation.ca

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Part I: Hereditary breast and ovarian cancer referral screening tool to identify patients most likely to benefit from referral to genetics

Part I of this tool is used to predict which individuals should be referred for genetic counselling due to increased risk for a hereditary breast cancer syndrome including but not limited to hereditary breast and ovarian cancer (HBOC) syndrome caused by mutations in *BRCA1* and *BRCA2* genes. Part II of this tool is used to identify individuals who are at high risk to carry a mutation in *BRCA1* or *BRCA2* genes.

1. Did any of your first degree relatives (parent, sibling, child) have breast *or* ovarian cancer?	Yes ❒	No ❒
2. Did any of your relatives have bilateral breast cancer?	Yes ❒	No ❒
3. Did any man in your family have breast cancer?	Yes ❒	No ❒
4. Did any woman in your family have breast *and* ovarian cancer?	Yes ❒	No ❒
5. Did any woman in your family have breast cancer before the age of 50 years?	Yes ❒	No ❒
6. Do you have 2 or more relatives with breast *and/or* ovarian cancer?	Yes ❒	No ❒
7. Do you have 2 or more relatives with breast *and/or* bowel cancer?	Yes ❒	No ❒

Management: **With 1 or more** positive responses, discuss referral to genetics

This POC tool is based on the Family History Screening-7 (FHS-7) (Ashton-Prolla *et al* 2009), which was designed for use in primary care settings and demonstrated an overall sensitivity of 97.0% and a specificity of 53.0% for HBOC syndrome. Overall, **using as cut point one positive answer**, the sensitivity and specificity of the instrument were 87.6% and 56.4%, respectively for hereditary breast cancer syndromes.

Reference: Ashton-Prolla P, Giacomazzi J, Schmidt AV, *et al*. Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. *BMC Cancer* 2009; 9:283

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Part II: Red Flags to identify patients at **high risk** of hereditary breast and ovarian cancer most likely to benefit from referral to genetics

These are general guidelines to identify patients at **high risk** for hereditary breast and ovarian cancer (HBOC) syndrome. You should consider referring your patient to your local genetics centre or hereditary cancer program for further assessment if s/he has a family or personal history of:

- Breast cancer diagnosis at a young age (<35-45 years) [both invasive and ductal carcinoma *in situ*]
- Ovarian cancer at any age [epithelial]
- Male breast cancer
- Multiple primaries in the same individual e.g. bilateral breast cancer (particularly if the diagnosis was before age 50), breast and ovarian cancer
- Breast cancer diagnosis **AND** a family history of two or more additional HBOC- related cancers, including breast, ovarian, prostate (Gleason ≥7) and pancreatic cancer
- High risk ethnicity (Ashkenazi Jewish, Icelandic) and a personal and/or family history of breast, ovarian or pancreatic cancer
- Triple negative breast cancer diagnosed <age 60

OR if s/he has a personal

- Probability of 10% or higher to carry a *BRCA* mutation

Eligibility criteria for genetic testing vary among organizations. In general, criteria are based on clinical features that increase the likelihood of a hereditary cancer susceptibility syndrome.

If possible, the affected individual in the family at highest risk to carry a mutation is offered testing first in order to maximize the likelihood of detecting a mutation.

Testing an unaffected individual should only be considered if an affected individual is not available for testing. There are significant limitations to interpretation of test results in an unaffected individual. Unaffected individuals can be referred for genetic counselling, risk assessment and information. It is important to note that any individual of Ashkenazi Jewish ethnicity or French Canadian ethnicities can be offered genetic testing for the mutations commonly found in these ethnic groups (e.g. three common mutations in those of Ashkenazi Jewish ethnicity). A negative result in this situation only rules out those ethnic-specific mutations.

For more information on Hereditary Breast and Ovarian Cancer such as screening recommendations and references see the complete *GEC-KO Messenger* at www.geneticseducation.ca

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DIRECT TO CONSUMER GENETIC TESTING

Bottom line: Direct-to-consumer genetic testing (DTC-GT) is over-the-counter genetic testing available online to consumers through private companies. Generally, results report an individual's risk to develop a medical condition as being below average/low, average/general population, and above average/ high based on genome wide association studies (GWAS). Results may provide medically useful information for consumers and potentially provide support and motivation for lifestyle changes (e.g. weight loss, smoking cessation) or even more vigilant surveillance (e.g. breast cancer screening), reveal carrier status of single gene conditions (e.g. cystic fibrosis), effectiveness and side-effect risk of certain pharmaceuticals, in addition to medically irrelevant information (e.g. curly hair). Currently, DTC-GT is not regulated or accountable to an appropriate governing body. Numerous professional societies express concern about how DTC-GT is marketed to consumers, what and how information is provided and the lack of genetic counselling. **Family health history-based risk assessment is still the gold standard in initial assessment for heritable conditions.**

WHAT IS DIRECT –TO-CONSUMER GENETIC TESTING?

Direct-to-consumer genetic testing (DTC-GT), also referred to as personal genome testing, refers to genetic testing available for over-the-counter purchase without the requirement of health care provider involvement. Generally, DTC-GT is marketed with the promise of providing predictive genetic risk assessment for a variety of health conditions (e.g. diabetes, cancer, obesity) and information regarding response to and/or side-effect risk of certain pharmaceuticals (e.g. clopidogrel, statins). Increasingly personal genome testing companies are requiring provider involvement.

DTC-GT uses data generated from genome-wide association studies (GWAS). GWAS are case-control studies which examine many common variations in our genetic code (single nucleotide polymorphisms [SNPs]). They compare large groups of individuals (unaffected controls versus individuals with symptoms of a specific disease or those experiencing a particular medication response) in an attempt to distinguish between non-harmful changes in the DNA code and pathogenic, disease causing/predisposing changes. SNPs (pronounced 'snips') are the most common type of genetic variation. Each SNP represents a difference in a single DNA building block, a nucleotide. SNPs occur normally in an individual's genome about once in every 300 nucleotides, thus there are about 10 million SNPs in the human genome.

DTC-GT uses odds ratios and relative risks to categorize an individual as at increased risk (higher than average), average (general population risk), or at decreased risk (lower than average).

DTC-GT can also screen for single gene disorders (e.g. cystic fibrosis, *HFE*-associated hemochromatosis). Additionally, DTC-GT is advertised to assist in diet and exercise planning and can uncover medically irrelevant information such as bitter taste perception or curly hair.

Generally, DTC-GT is available online to anyone for a cost. Genetic testing for DTC-GT is usually performed on a saliva sample.

Appropriate pre- and post-test counselling is rarely offered by the DTC-GT company or accessed by consumers when available. Ideally, it should be carried out so that the consumer is informed of what the results might reveal (e.g. risk of multifactorial conditions that arise due to the combined contribution of genetic and environmental factors, carrier status of single gene conditions, including cancer predisposition syndromes) and the potential for results requiring additional medical follow-up not limited to behavioural modifications (e.g. vigilant breast screening and discussion of prophylactic surgery as a result of a *BRCA* gene mutation). The implications for extended family members should be addressed. Pre- and post-test genetic counselling has been demonstrated to aid in countering patient distress and encouraging patients to be proactive in their use of test results.

WHAT DOES THE GENETIC TEST RESULT MEAN?

While there are limited data to support the clinical validity (ability to predict clinical outcome) and utility (the likelihood of improving patient outcome), some consumers might benefit from DTC-GT as results may:

- Encourage positive behaviour modifications (e.g. increase exercise, smoking cessation)
  - Although, a recent longitudinal study demonstrated no differences between baseline and follow-up in consumer's dietary fat intake and exercise behaviour in response to DTC-GT results
- Provide useful information for medication choice, dose or management
- Provide information to individuals who have no or limited information about their family history (e.g. an individual who was adopted)
- Reveal carrier status of a genetic condition that could have implications for family planning

Caution when interpreting DTC-GT should be exercised as:

- DTC-GT does not take into account numerous factors important when interpreting genetic test results such as age, family history, lifestyle (e.g. smoking, obesity) and other environmental factors that are a significant contribution to common complex disease development
- **Family health history-based risk assessment is still the gold standard in the initial assessment for heritable conditions**

The impact on a publicly funded health care system of the result of a privately obtained test that suggests additional follow-up (e.g. blood tests, colonoscopy) which is not otherwise indicated is unclear. There are limited prospective studies with actual DTC-GT consumers and longitudinal follow-up. Referral to a specialist or confirmation of test results in a clinical laboratory may be indicated in some circumstances to clarify appropriate surveillance and management.

Additionally, "misattributed equivalence" is a great concern associated with personalised genome testing. There is a fear that if a DTC-GT test were to indicate a lower than average lifetime risk for a certain condition, when family history indicated a much higher risk, a consumer could be falsely reassured and not be as vigilant about medical interventions indicated by family history. This phenomenon speaks to the need for knowledgeable health care provider involvement in pre- and post-test counselling. On the other hand, recognizing the limitation of self-reported family history (incorrect or incomplete information), there may be potential for DTC-GT to add to risk interpretation in some situations (e.g. response to and/or side effect risk of certain pharmaceuticals).

In Canada diagnostic laboratories are provincially regulated. At the time of writing, no DTC-GT is operating under approved provincial regulation, although some may meet USA federal standards (e.g. Clinical Laboratory Improvement Amendments, CLIA). Companies that are not regulated could have staff performance, test analysis and interpretation of results that may not be certified or licenced by any appropriate governing body.

Additionally, privacy is a major concern. DTC-GT companies have self-imposed policies that claim a consumer's genetic information will not be shared, although there is no regulation to dictate what happens if/when a company is sold or goes out of business. Patients should be advised to look into the privacy policy prior to purchasing DTC-GT.

RESOURCES

See www.geneticseducation.ca for more details and how to connect to your local genetics centre. To learn more about Canadian ethnicity-based carrier screening recommendations see the point of care tool

For a recent review on DTC-GT see Scott Roberts *et al*. Direct-to-Consumer genetic testing and personal genomics services: a review of recent empirical studies. *Curr Genet Med Rep.* 2013; 1(3): 182–200

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NON-INVASIVE PRENATAL TESTING

Non-Invasive Prenatal Testing (NIPT) is a screening test to prenatally detect Down syndrome and other aneuploidies. NIPT assesses fragments of cell-free DNA (cfDNA) that are circulating in maternal blood to determine if there is an increased chance that the fetus has aneuploidy. NIPT should be considered in pregnancies at increased risk of aneuploidy. NIPT has **higher sensitivity and specificity** for Down syndrome (trisomy 21) and trisomy 18 than current screening tests – First Trimester Screening (FTS)/Integrated Prenatal Screening (IPS)/ Maternal Serum Screening (MSS) - however **it is not considered to be diagnostic.** Positive results should be confirmed by diagnostic testing (amniocentesis or chorionic villus sampling) prior to any irrevocable action. Negative results may indicate additional follow-up testing and consultation. Women who do not meet criteria can pay for NIPT themselves. Price varies by company (~500$).

WHAT IS NON-INVASIVE PRENATAL TESTING?

Non-invasive prenatal testing (NIPT) is a **highly sensitive and specific** way to **screen** for particular chromosome aneuploidies (an abnormal chromosome number (extra or missing)), in particular trisomies 13, 18 and 21/Down syndrome. NIPT can also be used for sex chromosome identification for the purpose of fetal sex determination where there is increased risk for an X-linked disorder or a sex chromosome abnormality.

NIPT assesses fragments of cell-free DNA (cfDNA) derived from the placenta that are circulating in maternal blood and represent the fetal genetic profile. CfDNA from the pregnancy comprises approximately 10% of DNA in maternal blood and the amount increases with gestational age. Companies offering NIPT use various technologies to analyze cfDNA. Some detect higher relative amounts of DNA from an aneuploid fetus by comparing quantity to a reference chromosome, determining if there is a normal, higher or lower than expected quantity of particular DNA sequences found on select chromosomes (13, 18, 21, X, Y). Others sequence and analyse single-nucleotide polymorphisms (SNPs) to differentiate between maternal and fetal genotypes. **NIPT is a non-invasive test performed on a maternal blood sample that poses no risk to pregnancy.** Testing can be carried out as early as 9 weeks gestation. A dating ultrasound is recommended prior to drawing the blood sample to ensure viability, obtain an accurate gestational age, and to exclude multiple pregnancies.

NIPT validation studies in high risk populations have demonstrated high pick-up rates/sensitivity for the detection of Down syndrome (sensitivity 99-100 %), trisomy 18 (sensitivity 97-100%), trisomy 13 (sensitivity 79-92%) and sex chromosome differences. False positive rates are reported to be less than 2% overall. Early studies suggest that the positive predictive value (PPV) of NIPT in an unselected, general obstetrical population (low risk) is about 45% for Down syndrome (versus about 4% for standard screening) and about 40% for trisomy 18 (versus about 8% for standard screening). The PPV appears to be significantly higher in high risk populations. A number of women (<6%) have required a repeat blood draw due to initial test failure. Most studies have commercial affiliations.

At the present time, it is recommended that all women under age 40 at estimated date of birth (EDB) be offered prenatal screening, using FTS, IPS or MSS. If a woman is screen positive, NIPT may be considered as a secondary screen of higher sensitivity. Women 40 years or older at EDB can be offered NIPT as a first screen for aneuploidy. **NIPT is not a replacement for diagnostic prenatal testing.** A positive NIPT result should be confirmed by diagnostic testing (amniocentesis or chorionic villus sampling [CVS]) prior to any irrevocable action. The expected benefit of NIPT will be fewer women undergoing secondary invasive diagnostic tests associated with a risk of pregnancy loss.

NIPT is ordered by a healthcare professional. Some genetics centres are counselling patients about this testing option, and some are also organizing testing for patients who have been referred because of a high risk indication. All patients should have pre- and post-test counselling to ensure informed decision making and follow-up.

RED FLAGS TO CONSIDER TESTING OR GENETIC CONSULTATION

NIPT has been validated for use in women determined to be at high risk of having a fetus with certain aneuploidies (trisomy 13, 18, 21 and X and Y detection). Consider discussing NIPT as an option for women who:

- Are of advanced maternal age, defined as 40 years of age or older at EDB
- Have an abnormal serum screen i.e. FTS/IPS/MSS
- Have a fetal nuchal translucency (NT) measurement of 3.5mm or greater
- Have had a previous pregnancy or child with aneuploidy
- Have fetal congenital anomalies on ultrasound highly suggestive of trisomy 13, 18 or 21
- Have soft markers on ultrasound which are highly suggestive of aneuploidy [*Refer to SOGC guidelines, 2005*].
- Are at risk of carrying a male fetus with an X-linked condition (NIPT would be used for sex determination)

As each prenatal genetics centre has variable referral criteria and practice, abnormalities seen on ultrasound (e.g. congenital anomalies, NT ≥ 3.5mm or other soft markers) should be discussed with your local genetics centre to decide whether a referral is appropriate, whether NIPT should be offered first, or if additional testing should be considered.

WHAT DOES THE TEST RESULT MEAN?

Depending on the company, results may be worded as: positive or negative; aneuploidy detected, no aneuploidy detected or aneuploidy suspected/borderline value; or high risk or low risk.

Results typically take approximately 8-10 days.

If the result is negative, this is reassuring, however NIPT cannot:

- detect aneuploidy other than chromosomes 13, 18, 21, X and Y
  - some companies are now adding screening for other trisomies and certain microdeletion syndromes, addition of these rare conditions to the test increases the false positive rate and decreases the positive predictive value
- completely rule out aneuploidy
- detect single gene conditions
- detect congenital anomalies

Your patient should still be offered:

- a fetal morphology scan at 18-20 weeks gestation
- a referral for genetic and/or maternal fetal medicine consultation, which may be indicated for additional counselling and testing, depending on the reason your patient qualified for NIPT
- *As per SOGC guidelines, MS-AFP should only be offered to pregnant women with a pre-pregnant body mass index ≥ 35 kg/m^2 or when geographical or clinical access factors limit timely and good quality ultrasound screening*

If the result is positive, follow-up genetic counselling is indicated and confirmation by diagnostic testing should be offered. The SOGC and numerous North American Genetics societies/colleges recommend that **no irrevocable obstetrical decisions should be made in pregnancies with abnormal NIPT results without confirmatory invasive testing** (amniocentesis or CVS) as false positive results do occur.

Important pre- and post- test counselling considerations around a positive result are:

- While a highly sensitive and specific screen, the likelihood that a positive aneuploidy result is truly positive for an aneuploidy other than Down syndrome is low (e.g. trisomy 13, a sex chromosome aneuploidy) (<60%). Data are still emerging on the positive predictive value of NIPT.
- NIPT screens for more than one condition and it is possible to receive an incidental finding. For example, the test could be ordered because of an increased fetal risk for Down syndrome and the report could indicate suspicion of another chromosome abnormality, e.g. suspected sex chromosome aneuploidy, like Turner syndrome (45,X) or Klinefelter syndrome (47,XXY).

For a recent review on NIPT see Cuckle H, *et al*, Cell-free DNA screening for fetal aneuploidy as a clinical service, *Clin Biochem (*2015), http://dx.doi.org/10.1016/j.clinbiochem.2015.02.011

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PRENATAL CHROMOSOMAL MICROARRAY

Chromosomal microarray (CMA) is a high resolution genomic test to assess very small gains and losses (copy number variants, CNV) of chromosomal information in an individual or pregnancy. CMA is expected to replace standard karyotyping for invasive prenatal testing investigations because of its increased diagnostic yield.
When CMA should be considered in the prenatal setting is controversial. In general CMA should be offered in cases where ultrasound or fetal MRI has revealed structural abnormalities. Patients should receive comprehensive pre-test and post-test counselling by a qualified healthcare professional (e.g. genetic counsellor or geneticist) so that the benefits, limitations and possible outcomes of the analysis can be discussed in detail.
Results may be normal (no significant CNV detected), abnormal (pathogenic CNV detected with known clinical consequence which can include a range of physical, developmental and mental health issues), a variant of unclear clinical significance (VUS, a CNV with unknown clinical consequences) or an incidental finding (a finding unrelated to the initial reason for testing e.g. carrier status for a recessive condition).

WHAT IS CHROMOSOMAL MICROARRAY?

Chromosomal microarray (CMA) is a cytogenetic test used to determine if there are chromosomal imbalances, either large (*e.g. whole extra or missing chromosomes,* also detected by standard karyotype) or smaller extra (*micro-duplication*) or missing (*micro-deletion*) pieces of genetic information, also called copy number variants (CNV). Micro-duplications or micro-deletions may be associated with significant health and/or developmental problems despite their small size. See more on CMA for paediatric indications here.

Copy number variants (CNV) make an important contribution to genetic variation and human disease and may comprise about 13% of the human genome. CNVs can be inherited or *de novo*.

A CNV which is known to cause health and/or developmental problems is called "pathogenic". The true extent of consequences related to a CNV depends on the particular gene(s) lost or gained and how gene function is altered when present in a different copy number. Depending on the indication for CMA, the chance of finding an abnormal result varies. About 1-2% of pregnancies, where the only indication for invasive prenatal testing is advanced maternal age, will have a clinically significant finding on CMA following a normal karyotype (consistent with the general population prevalence of CNV). About 6.5% of pregnancies, where a single ultrasound abnormality is detected, will have a clinically significant finding on CMA following a normal karyotype.

A CNV whose clinical significance is not clear is called a "variant of uncertain/unclear significance" (VUS/VOUS). This is a genomic variant that has not yet been categorized as benign or pathogenic, either because too few cases have been reported in the literature or the affected gene's content and/or function are not yet understood. Some variants may be interpreted as 'likely pathogenic' or 'likely benign'. A VUS can be expected in about 1% of prenatal cases.

WHO SHOULD BE OFFERED PRENATAL MICROARRAY?

Indications for offering CMA to a patient in the prenatal setting vary regionally. Whether or not to offer CMA to all women having invasive prenatal testing or only to women who are at increased risk is controversial. Contact your local genetics centre to learn more about when CMA is offered to your patient population. In general, recommendations from Canadian professional societies (Canadian College of Medical Geneticists (CCMG) and Society of Obstetricians and Gynaecologists of Canada (SOGC)) state:

- CMA may be an appropriate investigative measure in cases with fetal structural abnormalities detected on ultrasound or fetal MRI
  - CMA is generally not recommended in pregnancies at increased risk for a numerical chromosomal abnormality (aneuploidy) e.g. associated with advanced maternal age, positive maternal serum screen. In these circumstances, current standard of care is to offer second tier screening such as non-invasive prenatal testing (NIPT) or diagnostic testing with QF-PCR, a technology which detects common aneuploidies: Down syndrome, Trisomy 18, Trisomy 13 and sex chromosome aneuploidies.
- CMA is also recommended for investigation of fetal demise or stillbirth.

Canadian guidelines strongly support patients receiving comprehensive pre-test and post-test counselling by a qualified healthcare professional (e.g. genetic counsellor or geneticist) so that the benefits, limitations and possible outcomes of the analysis can be discussed in detail.

WHAT DOES THE GENETIC TEST RESULT MEAN?

The classification of a CNV is based on size, inheritance, gene content and clinical relevance as determined by information in various databases (DECIPHER, OMIM) and published literature in addition to reference populations (public/private). Generally, there are four possible results of CMA testing. Patients should be counselled about all possible outcomes.

1. Normal Result

No clinically significant copy number changes were identified in the DNA of this specimen in the areas tested.

- What does this result mean?
  - Excludes a micro-deletion/micro-duplication (CNV) within the limits of resolution of the test (typically very high).
- What are the limitations of this result?
  - CMA is <u>not</u> able to detect balanced genomic rearrangements, low levels of mosaicism, and mutations within single genes, so a normal CMA result does not completely rule out a genomic abnormality.
- What are the next steps?
  - Even with normal CMA results, a referral for genetic consultation should be considered, depending on the initial reason for the invasive prenatal testing, so that additional genetic testing may be offered where appropriate. For example, if the ultrasound finding that triggered invasive testing was a cystic hygroma, your patient may be offered single gene testing for Noonan syndrome.

2. Pathogenic micro-deletion or micro-duplication (CNV)

A pathogenic CNV is known to be associated with an abnormal phenotype. There are over 200 known pathogenic CNVs and this number is increasing with CMA use.

- What does this result mean?
  - Provides insight to the genomic etiology of ultrasound findings and may assist in counselling about prenatal and postnatal outcomes and management options e.g. 22q11 deletion, also known as DiGeorge syndrome, characterized by congenital heart disease (74%), palatal abnormalities (69%); learning difficulties (70%-90%); immune deficiency (77%); hypocalcemia (50%); renal anomalies (31%); autism or autistic spectrum disorder (20% of children); psychiatric illness (specifically schizophrenia, 25% of adults).
  - May not be related to the ultrasound finding (see incidental findings) but may have implications for future care e.g. duplication of the *PMP22* gene causes Charcot-Marie-Tooth 1: additional family testing and screening and neurology consult in adolescence/early adulthood would be suggested
- What are the limitations of this result?
  - Not all pathogenic findings are associated with a severe clinical presentation, and the clinical presentation can be extremely variable. Uncertainty often remains and may cause anxiety for a pregnant couple.
- What are the next steps?
  - Genetic counselling is recommended to review significance of finding, provide information resources and support and, depending on the CNV, discuss further testing/change in medical management (e.g. fetal echocardiogram, delivery hospital choice) and discuss the implications associated with parental testing.

3. Variation of unclear clinical significance (VUS/VOUS)

- What does this result mean?
  - Not every CNV in the genome has been classified as yet as pathogenic or benign
  - A variant that has not been described in the literature is challenging to interpret. Knowledge of parental status will determine whether or not the CNV is familial, and less likely to be pathogenic, or *de novo* (new in the affected individual) and more likely pathogenic

- What are the next steps?
  - Parental samples should be obtained and analysed, then refer to genetics, if not already initiated

4. Incidental finding (IF)

- What does this result mean?
  - An IF is a genetic variant(s) – either benign or pathogenic - identified by a genetic test that is unrelated to the primary indication for testing. In the prenatal setting, IF more commonly refers to findings which do not have a direct consequence for the fetus, but may have implications postnatally for the individual or for his/her relatives (see example of Charcot-Marie-Tooth disease in pathogenic CNV section above).
  - An IF may signify
    - Presence of late-onset disorder with result having clinical utility e.g. hereditary cancer syndrome
    - Presence of late-onset disease without therapeutic possibilities e.g. Alzheimer disease risk
    - Carrier status for autosomal recessive or X-linked diseases e.g. cystic fibrosis (CF), Duchenne Muscular Dystrophy (DMD)
    - Parental consanguinity
- What are the next steps?
  - Genetic counselling is recommended to review significance of finding, provide information resources and support and, depending on the CNV, discuss further testing or medical management recommendations.

RESOURCES

Unique – Disorder Guides - Unique has been collecting information about specific chromosome disorders in their offline database for nearly 30 years and produces family-friendly, medically-verified, disorder-specific information guides.

Orphanet - A reference portal for information on rare diseases and orphan drugs, for all audiences

Visit www.geneticseducation.ca to connect to your local genetics centre. A more comprehensive GECKO Messenger which includes references and accompanying patient handout coming soon. You may also wish to consult your local maternal-fetal medicine (MFM) specialist or high risk obstetrician/gynaecologist depending on the reason CMA has being considered. If there are terms that require further elaboration please visit the GEC-KO Glossary in Educational Resources.

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CONSANGUINITY

Consanguinity is defined as a union between two individuals who are related as second cousins or closer. The chance for adverse outcome in the offspring of a consanguineous union is an estimate based on family history, degree of consanguinity and background population risk. In general, studies have shown that, when there is no known genetic diagnosis in the family, first cousin unions are at a 1.7-2.8% additional risk above the general population risk of 2-3% to have offspring with a congenital anomaly. The risk for a more closely related union is higher and for a more distantly related union is lower. The best tool for counselling a couple about consanguinity is a detailed family history. Genetic testing based on ethnicity, and standard prenatal screening should be offered as for non-related couples. Referral for genetic consultation can be considered if appropriate based on family history and/or screening results.

WHAT IS CONSANGUINITY?

One billion of the current global population live in communities with a preference for consanguineous union. Consanguinity is defined as a union between two individuals who are related as second cousins or closer.[1]

In North African, Middle and West Asian, and South Indian populations (and immigrants from these communities) about 20-50% of all unions are consanguineous and first cousin unions account for about 1/3 of all marriages. Reasons for preferring a consanguineous union can include cultural continuity, family solidarity, or reduction of uncertainty associated with health and financial issues. Primary healthcare providers are likely to see couples in consanguineous unions from these communities who are seeking preconception/prenatal counselling.[1]

RED FLAGS TO CONSIDER TESTING OR GENETIC CONSULTATION[1,2]

- ✓ Take a detailed 3-4 generation family history
  - Offer referral to your local genetics centre if family history is positive for congenital anomalies, intellectual disability or suspected genetic condition, as with non-related couples
- ✓ Offer genetic screening based on ethnicity
  - Offer referral to your local genetics centre if both members of the couple are carriers of the same condition, or if both are carriers of a hemoglobinopathy, even if each is a carrier of a different type of hemoglobinopathy, as with non-related couples
- ✓ Offer standard prenatal care and pediatric follow-up

WHAT DOES CONSANGUINITY MEAN FOR MY PATIENT?

The chance for adverse outcome in the offspring of a consanguineous union is not an absolute number but rather an estimate based on family history, degree of consanguinity and background population risk.[2]

In general, studies have shown that, when there is no known genetic diagnosis in the family, first cousin unions are at a 1.7-2.8% additional risk above the general population risk of 2-3% to have offspring with a congenital anomaly, for example a congenital heart defect, which is the most common multifactorial congenital anomaly[1,2]. The risk for a more closely related union is higher and for a more distantly related union is lower. There is an increased risk of autosomal recessive conditions in the offspring of consanguineous unions. The closer the biological relationship between the couple, the higher the chance their offspring will inherit identical copies of one or more detrimental recessive genes from each parent[1]. It is unclear whether consanguinity increases the risk for later onset complex disorders such as diabetes or cardiovascular disorders[1,2].

There is a 3.5-4.4% increased risk (above population risk) for children of consanguineous unions to die before the age of 10 years. [1,2].

The first step and best tool for counselling a couple with consanguinity involves taking a detailed family history. A four-generation pedigree is ideal for documentation and discussion with the patient[1,2]. Patients can confuse familial relationships such as second cousins with first cousins once removed, and, in some cultures, non-biological relatives may be referred to as "uncle" or "aunt" and can be confused with blood relatives[2]. Download the GEC-KO Family History Tool to assist you in eliciting and drawing the family history.

When taking the family history, be specific in your questions and note:

- Offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins of your patient, as appropriate
- Ethnicity of all grandparents
- Congenital anomalies or birth defects
- Early hearing and/or vision impairment
- Failure to thrive
- Intellectual disability, learning disability, developmental delay or regression
- Inherited blood disorders (e.g. thalassemia)
- Unexplained neonatal or infant death
- Seizure disorder
- Undiagnosed severe conditions

Ethnicity-based Screening

Certain genetic disorders are more common in populations likely to prefer consanguineous unions (e.g. hemoglobinopathies). Screening for carrier state is recommended in the Canadian Guidelines for Prenatal Diagnosis for individuals belonging to population groups known to have an increased risk for carrying certain genetic disorders. Preconception counselling and testing is recommended in order to arrange for prenatal testing if appropriate.[3] See the GEC-KO Point of Care Tool for more on ethnicity-based screening recommendations in Canada.

Hemoglobinopathies

Hemoglobinopathies are a group of inherited disorders that result in abnormal production of the hemoglobin protein due to mutations in the genes responsible for the protein's building blocks, α-globin and/or β-globin. **It is recommended that all pregnant women from an ethnic background at increased risk of hemoglobinopathy and/or thalassemia be screened by both CBC, to assess the MCV and MCH, and hemoglobin electrophoresis or high performance liquid chromatography (HPLC).**[4] If both individuals of a couple are found to be carriers of a hemoglobinopathy (even if each is a carrier of a different type of hemoglobinopathy), referral for genetic consultation and possible genetic testing is strongly recommended.

Contact your local genetics centre to learn more about the community you serve and if there is an at-risk population you should be considering for referral for genetic consultation (e.g. individuals from Saguenay-Lac-St-Jean/Charlevoix regions of Quebec).

References

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[3] Chodirker BN, Cadrin C, Davies GAL, *et al*. Canadian guidelines for prenatal diagnosis. Genetic indications for prenatal diagnosis. SOGC Clinical Practice Guideline No. 105, June 2001. *J Obstet Gynaecol Can* 2001;23:525–31

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Resource: Consanguinity/Endogamy Resource http://consang.net

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