Medical Genetics in Primary Care

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Clinical Geneticist
Medical Genetics RCPSC residency program director
Objectives

• Introduction to Medical Genetics Clinic: Who we are and What we do

• Indications for Genetics referrals throughout the lifespan

• Provide resources (local and online)
Relevance to Primary Care

- 1/10 patients seen by primary care physicians have a condition with a genetic component

- Patients have access to online information and will expect their primary care physicians to be informed

- Rapid advances in genetic knowledge and testing with quick translation into clinical care

- Personalized Health care (Precision medicine)
A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.°

— President Barack Obama, State of the Union Address, January 20, 2015

is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice.

The proposed initiative has two main components: a near-term focus on cancer and a broader

Precision medicine is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative® will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.
What to know?

American Academy of Family Physicians
Recommended curriculum guidelines: Medical Genetics
Online (skills, knowledge, attitudes)

“Developing a curriculum statement based on clinical practice: genetics in primary care”
S Burke et al., J of General Practice, 2009,59:99-103
Box 1. The key themes supporting the RCGP curriculum statement *Genetics in Primary Care* and an overview of the associated learning outcomes.

- Identifying patients with, or at risk of, a genetic condition.
  - Knowledge of genetic basis and clinical features of common and/or important conditions.
  - Ability to take and interpret family history information.
  - Understand how genetic changes may cause disease.
  - Recognise patterns of inheritance (single gene, chromosomal, and multifactorial).
  - Awareness of genetic implications of antenatal and neonatal screening programmes.
Box 1. The key themes supporting the RCGP curriculum statement *Genetics in Primary Care* and an overview of the associated learning outcomes.

- Clinical management of genetic conditions.
  - Describe local and national referral and management guidelines for patients with genetic conditions.
  - Able to access specialist help and advice from genetic services and refer appropriately.
  - Awareness of management options (reassurance, managing uncertainty, reproductive options, preventative measures, and surveillance).
  - Able to provide and coordinate patient-centred care including an awareness of patient support groups.
  - Awareness of different uses of genetic tests (diagnostic, predictive, and carrier testing) and potential emotional, ethical, legal, and social issues associated with these.
Box 1. The key themes supporting the RCGP curriculum statement *Genetics in Primary Care* and an overview of the associated learning outcomes.

- Communicating genetic information.
  - Ability to communicate genetic information in an understandable, non-directive manner.
  - Appreciate the emotional, ethical, legal, and social impacts of genetic information on patients and their families.
# Medical Genetics clinic

## Who we are...

<table>
<thead>
<tr>
<th>Clinic Team</th>
<th>Medical Geneticists</th>
<th>Genetic counsellors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training</td>
<td>MD + RCPSC 5-year residency in Medical Genetics</td>
<td>MSc in Genetic counselling</td>
</tr>
<tr>
<td></td>
<td>or 2-3 year fellowship in Medical Genetics</td>
<td></td>
</tr>
<tr>
<td>Number in Calgary</td>
<td>10</td>
<td>10-12</td>
</tr>
</tbody>
</table>
Who we are
Medical Genetics: southern Alberta

• Outpatient clinics and inpatient consultations
• Clinics are based at Alberta Children’s Hospital and TRW building (prenatal)
• Half our patients are adults
• Outreach clinics: Red Deer, Lethbridge, Medicine Hat
What do we do in our clinics?

• Consultants
• Goal is diagnosis and counselling regarding prognosis, future care and implications for others in the family

• Medical History
• Family history
• Physical examination

• Genetic testing
• Counselling
• Provide recommendations to primary care physician
| Before visit | Request for child’s medical charts; neurodevelopmental test results; all medical test results; copies of MRI, CT, or other imaging studies  
Request to bring photographs of child and family members  
Asked about the family history  
Asked to set aside sufficient time for prolonged consultation |
| At the visit | Clarify the purpose of the visit  
Review the child’s medical history and neurodevelopmental status  
Review family history (≥3 generations)  
Complete physical and neurologic examinations  
Geneticist’s initial impressions discussed |
| After the visit | Clinical photographs  
Laboratory studies (blood and/or urine tests)  
Arrangements for MRI or CT studies  
Arrangements for other consultations (eg, neurology, developmental pediatrics, ophthalmology, etc)  
Arrangements for ongoing communication and follow-up visits |
Clinical Genetics

Who are we?
What do we do?

Outpatient Clinics
- General Genetics
- Prenatal Genetics
- Metabolics
- Neurogenetics
- Cancer Genetics
- Other: cardiovascular, connective tissue disorders, ophthalmologic genetics

Inpatient Consults
- Prenatal
- Neonatal
- Pediatrics
- Adults

Diagnostic Labs
- Cytogenetics
- Molecular
- Biochemical
Typical indications for a genetics referral

All life-stages!

- Preconception
- Fetal /Prenatal
- Neonatal/Pediatric
- Adult
# Preconception referrals

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier testing based on ethnic background, ex: Thalassemia, hemoglobinopathies, A Jewish panel</td>
<td>Carrier testing to identify couples at 25% risk of having an affected pregnancy/child, discuss inheritance and risk</td>
</tr>
</tbody>
</table>
| Family history of a known condition  
  -ex: niece with cystic fibrosis  
  -ex: sister with a chromosome translocation | Attempt to obtain familial gene test result and offer carrier testing, discuss inheritance and risk, depending on condition and mode of inheritance |
| Consanguinity                                                            | Obtain family history to identify known conditions  
  Discuss double baseline risk (from 2-3% to 4-6%) of health issue, make recommendations |
| Previous abnormal fetus or another child with anomalies or health issues  | Review records or examine child to try and make a diagnosis to clarify recurrence risks and any specific prenatal testing |
| Maternal medication use                                                  | Teratogen review and counselling |
Prenatal referrals (same as preconceptional +)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive first trimester screen</td>
<td>Discuss implications and further testing options (ex: NIPT, invasive testing, etc)</td>
</tr>
<tr>
<td>Ex: risk of 1/50 for trisomy 21</td>
<td></td>
</tr>
<tr>
<td>Prenatal ultrasound soft markers</td>
<td>Discuss implications and further testing options (ex: NIPT, invasive testing, etc)</td>
</tr>
<tr>
<td>Ex: choroid plexus cyst</td>
<td></td>
</tr>
<tr>
<td>Fetal anomalies on ultrasound</td>
<td>Geneticist reviews images with MFM, obtains full history and family history, may examine parents, discusses possible diagnoses and testing options</td>
</tr>
<tr>
<td>Ex: cardiac anomaly</td>
<td></td>
</tr>
<tr>
<td>Maternal condition confirmed or suspected</td>
<td>Geneticist: Physical examination, review history and appropriate surveillance, discuss risk to mother and to pregnancy and available prenatal testing options</td>
</tr>
<tr>
<td>Ex: Ehlers Danlos syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Case 1

• Couple seen at 12 5/7 weeks gestation for a positive first trimester screen with a 1/5 risk for trisomy 21.

• Meet with genetic counsellor who reviews this result, obtains pregnancy and family history and discusses risk, additional screen or testing options.
Positive first trimester screen

• Prenatal testing/screening options

  1- NIPT

  2- invasive test, CVS at 11-14 weeks and amniocentesis at and after 15 weeks

  3- detailed scan at 18 weeks
Positive first trimester screen

• Prenatal testing/screening options

1- NIPT
NIPT
Non invasive prenatal testing

• Advanced **screen** for common trisomies (trisomy 21, 18 and 13)

• It is not a diagnostic test

• Different methods to assess relative amounts of chromosomes using cell-free DNA (cfDNA) present in maternal plasma

www.Ineogene.com
How does non-invasive prenatal testing compare to traditional prenatal screening for Down syndrome?

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Test info</th>
<th>Detection rate / Sensitivity for T21&lt;sup&gt;1&lt;/sup&gt;</th>
<th>False Positive Rate for T21&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Positive predictive value for T21&lt;sup&gt;2,3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS</td>
<td>MA, NT, PAPP-A, beta-hCG</td>
<td>80-85%</td>
<td>3-9%</td>
<td>~4%</td>
</tr>
<tr>
<td>IPS</td>
<td>MA, NT, PAPP-A, AFP, uE3, hCG</td>
<td>85-90%</td>
<td>2-4%</td>
<td>~4%</td>
</tr>
<tr>
<td>Quad/MSS</td>
<td>MA, AFP, uE3, total hCG, inhibin</td>
<td>75-85%</td>
<td>5-10%</td>
<td></td>
</tr>
<tr>
<td>NIPT</td>
<td>+/-MA, cfDNA</td>
<td>&gt;99%</td>
<td>0.1-0.2%</td>
<td>~80.9% for all populations (high and low risk women)</td>
</tr>
</tbody>
</table>

1 Prenatal Screening Ontario

Gec-ko geneticseducation.ca
Positive first trimester screen

• Prenatal testing/screening options

2- invasive test, CVS at 11-14 weeks and amniocentesis at or after 15 weeks
Chorionic villus sampling

- 11-14 weeks
- 1/100 risk of miscarriage
Amniocentesis

- 15 weeks and later
- 1/200 risk of miscarriage
# Testing on Prenatal sample

## Chromosome tests

**RAD**: Rapid aneuploidy detection
- assesses for trisomy 21, 18, 13 and sex chromosomes
- result in 2-3 working days

- **Array CGH** (replaced karyotype)
  - only done if fetal anomalies +/- growth
  - NT\(\geq 3.5\)

## Gene tests

**Gene tests**

(molecular tests) ex: CF, Fragile X, Duchenne. etc

- Need to know what condition/syndrome to test and target the gene

Only done if there is a family history or a clinical suspicion
Positive first trimester screen

• Prenatal testing/screening options

3. Detailed scan at 18 weeks

Will look for soft markers and any fetal anomalies. A normal ultrasound reduces the risk by 50% for trisomy 21.

-Half of patients with Down syndrome have a normal detailed prenatal ultrasound
Case 1

• Couple decides to have NIPT, result in 10 days, reassuring, low risk for trisomy 21.

• The 18 week detailed ultrasound demonstrates a cardiac anomaly with decreased LVOT and VSD suspected.

• An echocardiogram is done at 20 weeks, narrow aortic arch and VSD
Referred back to genetics to discuss potential causes

<table>
<thead>
<tr>
<th>Multifactorial</th>
<th>Chromosome</th>
<th>Single gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most likely</td>
<td>A few percent risk</td>
<td>Rarer</td>
</tr>
<tr>
<td>Combination of genetic and non-</td>
<td>Could be</td>
<td>No specific genetic syndrome</td>
</tr>
<tr>
<td>genetic factors</td>
<td>→ trisomy 21</td>
<td>If enough clinical features for a diagnosis,</td>
</tr>
<tr>
<td></td>
<td>→ Turner syndrome</td>
<td>can target testing</td>
</tr>
<tr>
<td></td>
<td>→ other chromosome deletion or duplication</td>
<td>(ex: Noonan syndrome)</td>
</tr>
<tr>
<td></td>
<td>Invasive test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ RAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ array CGH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No specific test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarify after birth when other-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wise normal exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR 2-4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 1

- Counselling options including:

- No testing during pregnancy and continue with full examination after birth

- Invasive testing for chromosome testing

- Discuss options with regards to pregnancy termination
Case 1

- Couple chose to do an amniocentesis
- RAD was normal in 3 days
- Array CGH (back in 10 days) showed deletion 22q11.2 (previously known as DiGeorge syndrome or velocardiofacial syndrome)
- Couple met to discuss clinical features of this diagnosis and parents offered testing as well (10% a parent also has this)
- Continued pregnancy and all treating physicians informed: OB, neonatology, cardiology, certain precautions prior to surgery (immune studies, Calcium, etc).
- We would plan to follow after baby is born, and may offer follow-up in our genetics clinic and forward surveillance recommendations to pediatrician/family doctor
Normal Female - 46,XX

[Genetic diagram with chromosome numbers and symbols]

[Genetic map with markers and intervals]
Whole Genome Microarray
Comparative Genomic Hybridization (CGH)

Reference DNA

Test DNA

Mix

Block repeated sequences

Hybridize

Microarray with oligonucleotides
# Newborn/pediatric referrals

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive newborn metabolic screen</td>
<td>Metabolics clinic does a more specific test to clarify if truly abnormal, then discuss immediate treatment plan</td>
</tr>
<tr>
<td>Newborn with 1 or more - significant growth anomalies</td>
<td>Full evaluation and diagnostic testing, counselling, provide information to primary care physician</td>
</tr>
<tr>
<td>- congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>- neurological issues</td>
<td></td>
</tr>
<tr>
<td>- dysmorphisms</td>
<td></td>
</tr>
<tr>
<td>Child with the same as above</td>
<td>“</td>
</tr>
<tr>
<td>Child with failure to thrive</td>
<td>“</td>
</tr>
<tr>
<td>Child with developmental delay +/- autism (with dysmorphisms or anomalies)</td>
<td>“</td>
</tr>
<tr>
<td>Suspected recognized syndrome</td>
<td>“</td>
</tr>
</tbody>
</table>
Case 2

- 3 month old boy referred to the outpatient Genetics clinic for increased height, weight and HC. (>97%ile)
- Noted asymmetry, Left leg wider than right?
- Umbilical hernia
- ?syndrome
Case 2

- Pregnancy history: No concerns

- Delivery:
  - Born at 36 weeks, large at slightly over 97%ile
  - Had a few episodes of hypoglycemia but resolved
  - Went home after 5 days and doing well at home
Case 2

• Physical examination

• Growth parameters all slightly above 97%ile
• Ear- helical pits
• Asymmetry of legs, L>R wider and longer, no vascular or cutaneous findings.
• Arm also asymmetric L>R
• Consistent with hemihyperplasia
Case 2

• Impression:
• Beckwith Wiedemann syndrome

• Discuss this with parents, including typical clinical features
• Typically healthy
• 5-10% risk of embryonal tumours:
  → screen q3-4 months with blood AFP levels (until 4 years of age) and and abdominal u/s until 8 years
Given leg length discrepancy, refer to orthopedics
Case 2

• Most are sporadic genetic causes (methylation changes)
• Order test (done in molecular genetics lab)
• Result in 1 month, confirms clinical diagnosis

• Recurrence risk in future pregnancies is very low
• Provide recommendations to pediatrician or GP regarding ongoing surveillance
## Adult referrals

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as pediatric referrals</td>
<td>Full evaluation and diagnostic testing, counselling, provide information to primary care physician</td>
</tr>
<tr>
<td>Infertility/premature ovarian failure</td>
<td>“</td>
</tr>
<tr>
<td>Personal and family cancer history strongly suspicious for a genetic etiology</td>
<td>Cancer genetics clinic (very large, they have specific referring guidelines)</td>
</tr>
<tr>
<td>Personal and/or family history of cardiomyopathy or arrhythmia</td>
<td>Cardiac genetics clinic (large # referrals)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Discuss inheritance, gene results or testing, provide screening and treatment recommendations to primary care physician</td>
</tr>
<tr>
<td>Neurological issues suggestive of a genetic condition</td>
<td>Neurogenetics clinic: ex: ataxias Predictive testing for Huntington disease</td>
</tr>
<tr>
<td>Marfan syndrome, EDS, etc</td>
<td>Connective tissue clinic</td>
</tr>
</tbody>
</table>
Case 3

- 32 year old G3P3 seen in Cancer genetics clinic because her mother had bilateral breast cancer, first diagnosed at 36.
- Her sister had breast cancer at 37.
- Maternal aunt and maternal grandmother had ovarian cancer at 45
Case 3

• Suspect BRCA gene related cancer in this family

• Pre-test counselling about predictive testing for this patient.
Predictive testing

• Benefits:
  • more intense surveillance (breast MRI and mammogram)
  • Option for surgical prevention (salpingoopherectomy, mastectomy)

• Harm:
  • Anxiety and stress of this risk
  • Affect family dynamic
  • Insurance discrimination
Case 3

• To test, need to first test an affected person in the family to interpret the genetic result
• so need to arrange it with sister or mother first
• BRCA1 and BRCA2 gene testing (molecular, look at sequence and small deletions and duplications)
Case 3
Possible results with a molecular gene test

Abnormal result: confirms the diagnosis and then there is a test available for others (including those without cancer for predictive testing)

Normal result: Sensitivity is very high, but not 100%.
- May be a missed mutation in BRCA
- another causative gene not tested
- “familial” and not a single gene as the cause
- person tested does not have the BRCA mutation that is accounting for the cancers in the other family members. (important to choose best person to test)

Uncertain result: Lab not able to determine if normal or abnormal, can’t use to offer predictive testing to other family members
Ethical considerations of genetic testing

• Need to obtain informed consent for any genetic test
• Genetic results may have implications for others in the family
• Genetic testing is not done on children for adult onset conditions or for carrier status (only to know about reproductive risks)
How to discuss a genetics referral to your patient

Medical Home

• Educate and “activate” patient
  – “In order to address your question, I would like to refer to Medical Genetics.”
  – “In order to care best for your child, I would like Medical Genetics to help me with the following question: ______________.”
  – I understand you are not concerned, but in order to provide best care, I need _____ from Medical Genetics.
# Expected Benefits from Medical Genetics

<table>
<thead>
<tr>
<th>For child/patient</th>
<th>For families</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved health outcomes</td>
<td>Understanding that comes from genetic counseling</td>
</tr>
<tr>
<td></td>
<td>including family planning discussion</td>
</tr>
<tr>
<td>Improved health care and surveillance</td>
<td>Health care changes (for some)</td>
</tr>
<tr>
<td>Improved understanding of condition</td>
<td>Diagnostic testing for other family members, if</td>
</tr>
<tr>
<td></td>
<td>warranted.</td>
</tr>
<tr>
<td>Improved educational planning</td>
<td>Understanding of condition</td>
</tr>
<tr>
<td>End unwarranted medical testing and treatments</td>
<td>Social support and peer networking</td>
</tr>
</tbody>
</table>
Resources

- Websites for medical information

Gene Reviews (~650 genetic conditions)
http://www.ncbi.nlm.nih.gov/books/NBK1116/

Unique rare chromosome (patient handouts, useful for MDs, nice handout explaining array CGH test)

SOGC- Genetics section- Canadian website
(great for prenatal topics, preconception carrier testing, etc)

AAP-common pediatric genetics conditions
Educational resource
Slides, webinars and fact sheets

• Family History in Primary Care
• Genetic red flags in Well-Checks
• Genetic testing in primary care
• Ordering the right tests in primary care
• Metabolic screening
• Online resources
• etc
Indications for genetic referral: a guide for healthcare providers

Beth A. Pletcher, MD, Helga V. Tortiello, PhD, Sarah J. Noblin, MS, CGC, Laurie H. Seaver, MD, Deborah A. Driscoll, MD, Robin L. Bennett, MS, and Susan J. Gross, MD

Key Words: genetic screening, genetic evaluation, prenatal testing, preconceptional testing, genetic referral

Disclaimer: This guideline is designed primarily as an educational resource for medical geneticists and other healthcare providers to help them provide quality medical genetic services. Adherence to this guideline does not necessarily assure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient’s record the rationale for any significant deviation from this guideline.

Geneticists and genetic counselors are often asked what may be appropriate reasons for referral to a genetics service. The Professional Practice and Guidelines Committee of the American College of Medical Genetics has generated lists of the more common reasons for referral and provide them for use by genetics professionals and other healthcare providers for guidance. The lists are divided into pediatric, prenatal, and adult indications.

As genetic health professionals, we are frequently asked under what clinical circumstances a genetic consultation is warranted. Although there is a vast array of indications for referral, here are a number of common indications for a genetic office visit. These lists have been divided into pediatric, preconceptional/prenatal, and adult categories for simplicity’s sake; findings are paired with consultation objectives. These lists are clearly not intended to be exhaustive or comprehensive, but will hopefully serve as a guide for primary care providers who may have questions about specific clinical circumstances. As the field of genetics expands and genetic technologies uncover new genes and genetic associations on a weekly basis, these lists will quickly become outdated. However, for now, these may help to provide a framework for patient centered specialty referrals (Tables 1–3).
Genetics clinic contact

• Not sure about a referral? Call us!
• There is a geneticist on call (through ROCA) and genetic counsellor in the clinic to answer questions.

• Alberta Children’s Hospital
  (referrals for children and adults)
  403-955-7373
  Fax: 403-955-2701

Prenatal Genetics Clinic: 403-943-8375
• Questions?

• Mary Ann Thomas
maryann.thomas@ahs.ca
Summary

- Medical Genetics Clinic: Who we are and What we do

- Indications for Genetics referrals throughout the lifespan

- Resources