Family history is a risk factor for disease throughout all stages of life

- **Birth defects**
- **Blood disorders**
- **Diabetes**
- **Depression**
- **Alzheimer’s disease**
- **Osteoporosis**
- **Asthma**
- **Autism**
- **Cancer**
- **Heart disease**
Risk Factors for Disease

Genes, environment, and behaviors interact with each other to cause disease.

Family History

Genes
Behaviors
Environment
What is Family?
What is Family?

- Any individual who is *biologically* related.
  - Nuclear (immediate)
  - Extended

- First degree: parents, siblings, children
- Second degree: aunts, uncles, half-siblings, grand children, grand parents
- Third degree: often too distant to impact risk
2009 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

26% Lung & bronchus

<table>
<thead>
<tr>
<th>Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Brain/ONS</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

ONS=Other nervous system.
Source: American Cancer Society, 2009.
“The challenge is over one million people in the US carry mutations predisposing to cancers that are preventable or treatable at an early stage...but only 3% know it.”

- William Rusconi, Vice President of Marketing for Myriad Genetic Laboratories, Inc. in 2005
How can you...

- Identify who is at risk?
- Determine their level of risk?
- Ensure that they get appropriate preventive services?
- Ensure that they get appropriate follow up care?
- Improve community health outcomes and population health outcomes?
- Possibly even save health care resources?
In Michigan

Cancer Registry Chart Reviews (2003-2004)

- 853 charts reviewed of Michigan residents with cancer
- 82% documented presence or absence of family history of cancer
  - 30% had positive family history of cancer
  - Over 80% documented relationship to patient and gender of affected family member
  - Over 94% missing age of onset/diagnosis of affected family member’s cancer
Health Plan Chart Reviews (2005-2007)

- 668 charts (60% from Family Practice, 25% from Internal Medicine, 15% from Pediatrics)
- Providers are collecting family history information.
- 92% of charts documented family history
  - 42% documented family history of cancer
  - 93% documented relationship of affected
  - Over 98% of charts never documented age of onset of affected
Key Informants and Focus Groups: Family Health History Collection (2003-2008)

Common Themes Identified for Michigan Providers:

- Do not believe they see patients with high-risk cancer family history
- Do not feel confident in ability to identify high-risk family history
- Uncertain where to refer
- Would use a clinical decision tool in practice

- Multi-faceted, state-wide comprehensive program
- Translation of evidence-based recommendations for genetic tests into practice
  - USPSTF BRCA recommendations
  - EGAPP recommendations on Lynch syndrome
  - EGAPP recommendation on breast cancer gene expression profiling
- Evaluate effectiveness in changing provider knowledge, test use, insurance coverage

• Multi-faceted, state-wide comprehensive program authorized by the affordable care act
• Focus on Young Breast Cancer Survivors (under age 45)
  • USPSTF BRCA recommendations
  • NCCN Guidelines
• Evaluate effectiveness in changing provider knowledge, surveillance of BRCA ½ genetic test use, insurance coverage, health plan policy intervention
Impact: A reduction in the young breast cancer death rate and the ovarian cancer death rate

1. Documentation of key cancer family history and personal history elements to conduct risk assessment
2. Referrals to genetic counseling services of patients at high risk for deleterious BRCA mutations based on personal and/or family history of cancer
3. Appropriate BRCA testing with prior written informed consent explaining risks, benefits and limitations of BRCA testing and appropriate interpretation of test results
4. Provision of related clinical services/interventions for patients with a known deleterious BRCA mutation.
So what is your role?
Hereditary Colon Cancer Syndromes

Lynch Syndrome, Familial Adenomatous Polyposis, MYH Associated Polypsis, Others
Ms. Armstrong was seen in genetics clinic at age 28-year-old when she was recently diagnosed with rectal cancer. She reported an 8 month history of rectal bleeding which was diagnosed as being related to hemorrhoids.

There was no documentation of family history.

Genetics staff noted that family history was significant for colorectal cancer in a maternal grandfather at age 52 and “female cancer” in her mother at age 45. Information about compliance with colon screening in the family is limited.
Also called Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
Accounts for ~ 2-3% of all CRC diagnoses
Caused by mutations in one of several DNA mismatch repair genes (MMR genes)
Diagnosis can be at a younger age, but average age of onset is 61 y.o. (Hampel et al. 2005)
Autosomal Dominant
Highly penetrant (70-80%)
## Lynch Syndrome

Cancer Risks in Individuals with Lynch syndrome up to Age 70 Years Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>HNPCC</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
<td>46 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
<td>42.5 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2%-7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
</tr>
</tbody>
</table>

Lynch-Associated MMR Genes

- MSH2
- MSH6
- MLH1
- PMS2
EGAPP Review of Genetic Testing for Colorectal Cancer

- “found sufficient evidence to recommend offering genetic testing for Lynch syndrome to all individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives.”

- MSI and IHC are both effective screening methods – no optimal testing strategy was identified.

- American College of Medical Genetics and the American Society of Human Genetics issued a joint statement to support that MSI/IHC are cost effective methods and should be offered to CRC patients.
Microsatellite Instability (MSI)

- Short scattered repeats
- Repeated 10 to 100s of times
- Increased rate of mutation within these regions
- Result: MSI High or MSI Instable
- 95% of Lynch colon tumors will be MSI high

Immunohistochemistry (IHC)

- Tumor samples are stained to identify which MMR gene is not expressing a protein. The missing expression points to which MMR gene is not working.
Management of Lynch Syndrome: Colon Cancer Risk

- Colonoscopy every 1-2 years (20 and 25 yrs OR 10-years prior to the earliest diagnosis)
- Recommended over sigmoidoscopy due to predominance of proximal tumors
- Removal of polyps
- If colon CA is detected – surgical options discussed including colectomy
Management of Lynch Syndrome
Gynecological Cancers

- Annual pap and pelvic exam
- Annual transvaginal ultrasound and CA-125
- In-office endometrial sampling
- Beginning between age 30 and 35 years
- Efficacy of screening is unclear
- Prophylactic TAHBSO should be considered after childbearing is completed
Management of Lynch Syndrome
Gastric and Urinary Tract Cancers

- EGD screening is recommended when a family history of gastric cancer is present.
- Schulmann et al (2005) found that ~ 50% of small bowel cancers in individuals with Lynch Syndrome occur in the duodenum.
- Annual urine cytology can be considered for urinary tract cancers (not a proven technique for these families yet).
**Muir-Torre**
- Sebaceous neoplasms of the skin and one + Lynch-related cancer

**Turcot**
- CNS tumors (typically glioblastoma in Lynch Syndrome families) + Colon CA or polyps

**Individuals with two MMR mutations are reported; onset is prior to age 10 (colon CA and café au lait spots)**

Kruger et al; Eur J Hum Genet. 2007 Sep 12.
A Public Health Perspective

MSI in 1066 patients with newly dx. colon cancer; regardless of age or family history

MSI High
208 patients

IHC analysis in all 208

Mutation analysis of MLH1, MSH2, MSH6, and PMS2 (select pts)

21 mutations detected

23 mutations found in 1066 patients (2.2%)

IHC in 109

858 MSI low
109 of which have very suspicious family/clinical histories

IHC analysis in 109

5 abnormalities in IHC → mutation analysis carried out

2 germline mutations identified

117 Family members identified as “at-risk”
52 had mutations

No further action in 749

Hampel et. al. 2005; NEJM.
Familial Adenomatous Polyposis (FAP)

- >100 colorectal adenomatous polyps OR
- <100 colorectal adenomatous polyps AND a relative with confirmed FAP
- Hundreds to thousands of colon polyps are typical beginning at a mean age of 16 years
- Autosomal Dominant Inheritance
Polyps and cancer are considered inevitable
7% develop colon cancer by age 21
87% by age 45
93% by age 50
Gastric hamartomatous polyps (50%)
Gastric adenomatous polyps (10%)
Duodenum polyps (50-90%)
Small bowel malignancy (4-12%)
Polyps in the periampullary region (50%)
Obstruction of the pancreatic duct
**Extraintestinal manifestations**

- Osteomas
- Dental abnormalities (17%)
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- Benign cutaneous lesions
- Desmoid tumors (10%) – benign fibrous tumors that are clonal proliferations of myofibroblasts
- Adrenal masses (7-13%)
Other APC-related Conditions

• AFAP – multiple polyps and a family history of colon cancer dx. under age 60 with multiple polyps (can be clinically similar to HNPCC)

• Gardner syndrome
  • Colonic adenomatous polyposis
  • Osteomas
  • Soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors

• Turcot syndrome
  • Colonic adenomatous polyps and CNS tumors (usually medulloblastoma in FAP)
Genetic Testing in FAP

• Full gene sequencing detects up to 90% of mutations
  • Protein truncation testing (PTT)
  • Duplication/Deletion analysis

• Ashkenazi Jewish mutation (I1307K)
  • Increased risk of Colon CA (10-20% lifetime)
  • ~6% are carriers
  • Colonoscopy every 1-2 years starting at age 35
Surveillance

- Hepatoblastoma (birth to age 5)
- Sigmoidoscopy every 1-2 years beginning at 10-12 years of age
- Colonoscopy once polyps are detected
- Delay in colectomy for 10-20 year olds with polyps smaller than 6 mm
- EGD by age 25; repeated every 1-3 years
- Surveillance after colectomy
A rare recessive cancer condition called MYH-Associated Polyposis
MYH-Associated Polyposis (MAP)

- Multiple adenomatous polyps over the lifetime (10 to hundreds)
- Affected individuals may develop polyps or cancer early (20 to 50 yrs).
- Recessive
- ~ 1 in 100 individuals is a carrier
- Risk of polyps and cancer is increased in carriers
- over the general population but not as high as those with two mutations.
MYH-Associated Polyposis (MAP)

• Typically Familial Adenomatous Polypsis (FAP) or Attenuated FAP must be ruled out first through APC-gene testing.

• Management (no set guidelines exist as of yet)
  • Sigmoidoscopy or colonoscopy every one to two years, beginning at age 18 years
  • Colonoscopy annually once polyps are detected
  • Consider colectomy if polyps cannot be adequately managed through colonoscopy and polypectomy.

• The risk for extra-colonic tumors or disease manifestations has not yet been clarified.
Additional polyposis syndromes

• PTEN hamartoma tumor syndrome
  • Risk of benign and malignant tumors of the thyroid, breast, and **endometrium**
• Juvenile polyposis syndrome (JPS)
• Puetz-Jeghers Syndrome (PJS)
  • Hamartomatous gastrointestinal polyps
  • Mucocutaneous pigmentation in children
• Those you think have a disease
  • Screening/Imaging
  • Specialty consultation
  • Specialty Care if affected

• Those with diagnosed disease
  • Continued Surveillance
  • Follow up care

• Those you think have a syndrome
  • Genetic counseling with/without testing
  • Screening/Imaging
  • Specialty Consult
  • Specialty Care if affected
  • Family counseling and education
  • Community outreach and support
What risk category does this patient fall into?
Colorectal cancer in a first-degree relative (>age 60)
Same screening methods as average-risk individuals
Beginning at age 40, rather than age 50
Based on all cancer hx. = High Risk

- 2 sisters with endometrial cancer
- Paternal Aunt with ovarian cancer
- Father with colorectal cancer
- All Lynch-associated tumors
Have you ever seen a genetic counselor?

What is your relationship to the affected family members and how old were they at diagnosis?

Have you or a family member had any genetic testing?

Unfortunately this program does not cover high risk screening, but we will make sure you are in contact with the right resources.

What cancers are in your family?

Do you know that some cancers run in families? Is this something you’re worried about?

Does your family have the resources to pay for screening?
Hereditary Breast and Ovarian Cancer
A 39-year-old woman arrives in your office with her son, who is in need of a routine checkup. After addressing her concerns and vaccinating her son, you wish her well and on her way.

As you grab the doorknob to leave the exam room, she says “by the way, Kent’s uncle (my brother) was diagnosed with breast cancer last week (at age 42)...should I be worried?”
1. Tell her that there is simply no time to discuss this today, as this is a pediatric clinic. [choose here]

2. Ask more about her family history and tell her you’re not sure about male breast cancer – she should see her regular doctor. [choose here]

3. Provide the number for genetic counseling services and encourage her to schedule her first screening mammogram. [choose here]
Not the best choice

#1: You do not address her concerns at this appointment...

• Since you did not express any great concern at today’s visit, she is not concerned by her risk.
• She has regular mammograms, which are normal.
• At age 47 she develops abdominal discomfort and bloating.
• Imaging reveals stranding around the ovaries and suspicious lesions in the liver. She is diagnosed with stage IV ovarian cancer with positive lymph nodes and liver metastasis.

And...
She dies in hospice at age 49.
The Best Choice!

#2: Ask more about her family history and tell her you're not sure...

- Her mother was diagnosed at 68 years old.
- She reports no other family history until you specifically ask about paternal history.
- You review the importance of mammography and clinical breast exams beginning at age 40.
- You do not order genetic testing at this time, but you strongly encourage her to see her primary care physician to discuss this family history.

She follows up with her physician who refers her to Genetics Clinic.
She is focused on her mother’s history, but the paternal history is much more concerning.

It is recommended that her brother have BRCA1/2 testing.
The patient has a mammogram, which reveals a small suspicious lesion. It is removed and found to be DCIS. She will continue to be followed by a breast surgeon at a high risk breast clinic.

Her brother undergoes testing and is found to carry a BRCA2 mutation.

Your patient has site-specific BRCA2 testing for the familial mutation and is positive. She would like to discuss having her ovaries removed to reduce her risk.
Hereditary Breast and Ovarian Cancer (HBOC)

• Accounts for 5-10% of all breast cancers. (And ~20% of Ashkenazi Jewish women diagnosed under age 45.)

• Approximately 1 in 200 are carriers in the general population.

• Caused by mutations in the BRCA1 or BRCA2 genes.

* Prostate and pancreatic cancer risk is not specifically addressed by the USPSTF evidence based guidelines, but is commonly seen in families with BRCA mutations.
• The BRCA genes are autosomal dominant – meaning they are not located on the sex chromosomes.
• Both men and women can pass on changes in these genes to their children. Paternal history counts!
• General population risk for breast cancer is 1 in 8 or ~12%.

• **Age Cumulative Breast Cancer Risks Female BRCA carriers**

<table>
<thead>
<tr>
<th>Age</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yrs</td>
<td>3.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>40 yrs</td>
<td>19.1%</td>
<td>12%</td>
</tr>
<tr>
<td>50 yrs</td>
<td>50.8%</td>
<td>46%</td>
</tr>
<tr>
<td>60 yrs</td>
<td>54.2%</td>
<td>61%</td>
</tr>
<tr>
<td>70 yrs</td>
<td>85%</td>
<td>86%</td>
</tr>
</tbody>
</table>

• Men with BRCA1 or BRCA2 mutations have a 1.8% or 8% lifetime risk of breast cancer respectively (by age 80)
<table>
<thead>
<tr>
<th>Cancer</th>
<th>3rd Lifetime Cancer risk</th>
<th>2\textsuperscript{nd} Cancer Risk within 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Population</strong></td>
<td><strong>BRCA1/2 mutation carrier</strong></td>
<td><strong>General Population</strong></td>
</tr>
<tr>
<td>Breast</td>
<td>12%</td>
<td>36-85%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>20-45%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Slightly increased</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>20% Slightly increased</td>
<td></td>
</tr>
</tbody>
</table>
Comprehensive BRACAnalysis®
$3,340.00

Sequencing

BRCA1

BRCA2

5-Site Rearrangement

BRCA1

1. Dutch Ancestry: deletions in exon 13 and exon 22
2. European (primarily British) ancestry: duplication of exon 13
3. European ancestry: deletion of exons 8 and 9
4. Deletion of exons 14-20

Used with permission from Nancie Petrucelli, Karmanos Cancer Institute, Detroit, MI
Management of HBOC

Surveillance

• Clinical breast exam every 6 months beginning at age 25.

• Annual mammogram and breast MRI starting age 25 or 10 yrs younger than the earliest age of onset in the family.

• Breast ultrasound when needed.

• Concurrent transvaginal ultrasound and CA-125 every 6 months beginning at age 35. Best practice, however there is no evidence of efficacy in decreasing mortality.
Management of HBOC

Chemoprevention

Prophylactic Surgery

• Bilateral total mastectomy — decreases the breast cancer risk by 90%. Patient should be informed of this option.

• Bilateral oophorectomy after child bearing age — decreases the ovarian cancer risk by 90-96% and decreases the breast cancer risk by 50%. Patient should be informed of this option.
Management of HBOC

NEGATIVE / VARIANT OF UNCERTAIN SIGNIFICANCE TEST RESULTS

Surveillance

• Alternate mammogram and breast MRI starting age 25-35 or 10 yrs younger than the earliest age of onset within the family.

• Could consider annual transvaginal ultrasound and CA-125 for ovarian cancer screen. Best practice, however there is no evidence of efficacy in decreasing mortality.
Other Hereditary Breast Cancer Syndromes
Cowden Syndrome

- Increased risk for cancers -- breast, endometrial, and thyroid (non-medullary). Breast cancer risk 30-50%. Renal cell carcinoma risk increased to a lesser degree.
- Multiple lipomas (benign fatty tumors), hemangiomas.
- Macrocephaly (large head circumference).
- Higher incidence fibrocystic breast disease, fibroadenomas.
- Thyroid gland nodules (benign).
Cowden syndrome

Trichilemmomas and papillomatous papules
Cowden Syndrome Surveillance

- Annual breast cancer screen: mammography and MRI beginning at age 30-35 or 5-10 years before the earliest breast cancer in the family.
- For endometrial cancer (premenopausal women): annual blind suction biopsies beginning at age 35-40 or 5 years before the youngest endometrial cancer in the family.
- For endometrial cancer (postmenopausal women): annual transvaginal ultrasound with biopsy of suspicious areas.
- Annual thyroid palpation. Baseline thyroid ultrasound at age 18. Consider annual thyroid ultrasound.
- Annual urine analysis. Urine cytology and renal ultrasound if FHx for renal cell carcinoma.
• Li Fraumeni – early-onset breast cancer, soft tissue sarcomas, osteosarcomas, adrenocortical carcinomas, leukemia, brain tumors, and other cancers

• Puetz-Jeghers – breast cancer, benign ovarian tumors, testicular tumors, pancreatic cancer, hamartomatous polyps of the ureter, bladder, GI tract, renal pelvis, bronchus, and nasal passages. Melanin spots on lips, buccal mucosa and digits.
Discussion

• Are you identifying high risk patients?
• How can you better identify patients at risk?
• What tools exist to help you?
• What are you currently doing with high risk patients?
• Where can you refer patients for genetic services?
• Where can you turn for more information?
Are you identifying high risk patients?
How can you better identify patients at risk?

• American Medical Association: Family Medical History Templates

• US Surgeon General’s Family Health Portrait
  https://familyhistory.hhs.gov/fhh-web/home.action

• NCHPEG Core Principles in Family History Training

• Genetics in Primary Care Institute (GPCI)
  http://www.medicalhomeinfo.org/gpci.aspx
  http://www.medicalhomeinfo.org/GPCI.aspx#webinar
What tools exist to help you?

- MDCH Cancer Family History Guide
- Breast Cancer Genetics Referral Screening Tool (electronic) - Bellcross
  http://www.brcagenscreen.org/main/score_interpretation/
- Gail, Claus, and other risk models
What are you currently doing with high risk patients? Where can you refer patients for genetic services?

• **Michigan Cancer Genetics Alliance (MCGA)**
  • Directory of Cancer Genetics Services –
    https://www.migeneticsconnection.org/cancer/directory.html

• **Michigan overview of breast cancer genetic counseling and testing**
  • www.migeneticsconnection.org/brca

• **American College of Surgeons Commission on Cancer 2012 Standards**
Where can you turn for more information?

- Michigan’s Genetics Resource Center
  - www.migeneticsconnection.org

- Gene Reviews

- Michigan Department of Community Health Cancer Genomics Program
  - www.michigan.gov/genomics
  - Jenna McLosky, mcloskyj@michigan.gov, 517-335-8826

- Genetic Alliance
  - www.geneticalliance.org

- Human Genome Project Information

DO NOT USE… Up to Date OR Web MD for accurate and reliable information on genetics!