Update: Integrating Genetic and Genomic Medicine Processes for Systematic Identification of Heritable Neoplasias

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On Behalf of the Cancer Team

NHGRI Genomic Medicine Colloquium, Dallas, TX, Jan. 28-29, 2013

Some Topics Considered by the Cancer Team (GM II & III)

- Universal MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Resected Colorectal Cancers on Main Campus (Update from 1 Experienced and 1 Naïve Site)
- Implementation of MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Endometrial Cancers on Main Campus
- Systematic Standardized Screening for Heritable Pheochromocytoma and Paraganglioma
- Somatic Genomics

3-Year Experience on Uptake of a Prototype Cancer Family History Tool

Update: Universal Screening of All Colorectal Cancers for Lynch Syndrome

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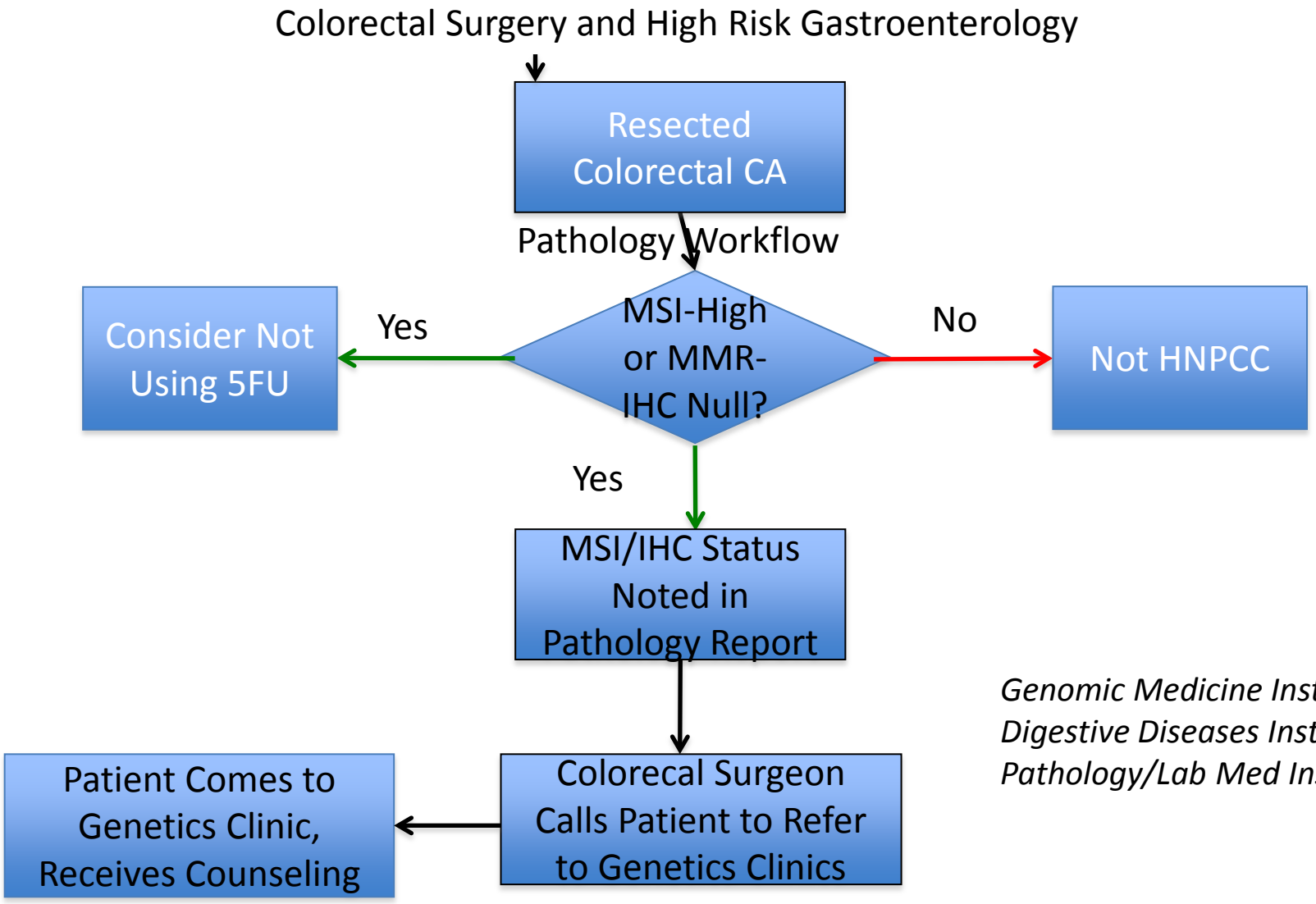
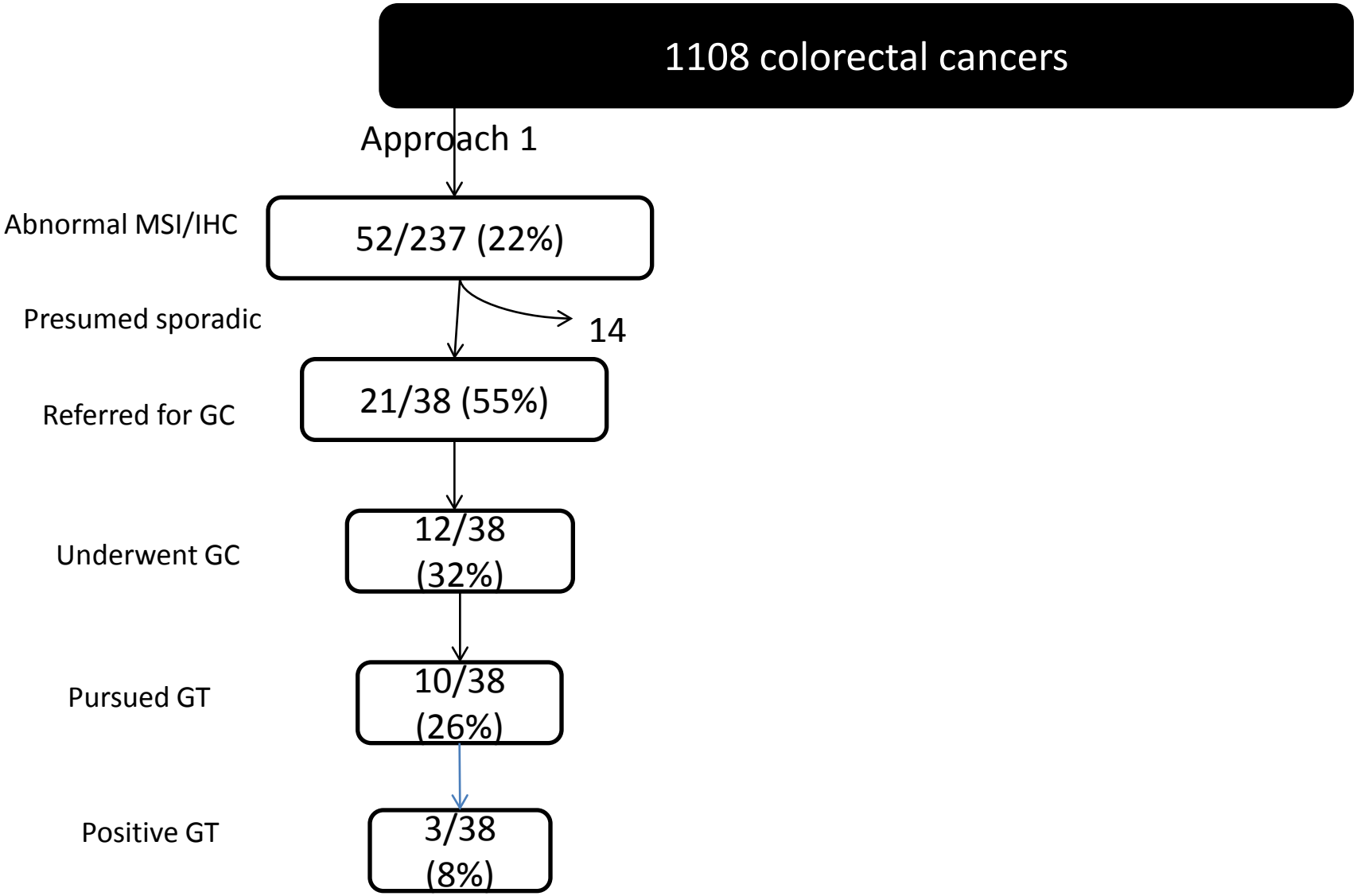
Quickie Reminder re Lynch Syndrome

- Most Common Adult-Onset Inherited Colorectal Cancer (CRC) Syndrome
  - Autosomal Dominant Inheritance
  - Caused by Germline Mutations in Mismatch Repair Genes (MMR)
  - High Risk of Colorectal, Endometrial and Other Cancers
  - Lynch Syndrome Diagnosed in 3-5% of all CRC Presentations
- Cellular Phenotype of Lynch-CRC
  - Microsatellite Instability (MSI)
  - MMR Protein Null (IHC detectable)
- Making Lynch Dx Changes Management for Patient and Mutation Positive Family Members
- Would Meet One of 2 Genomics Agenda Items of Healthy People 2020

Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2004.1-2007.7) = Approach 1



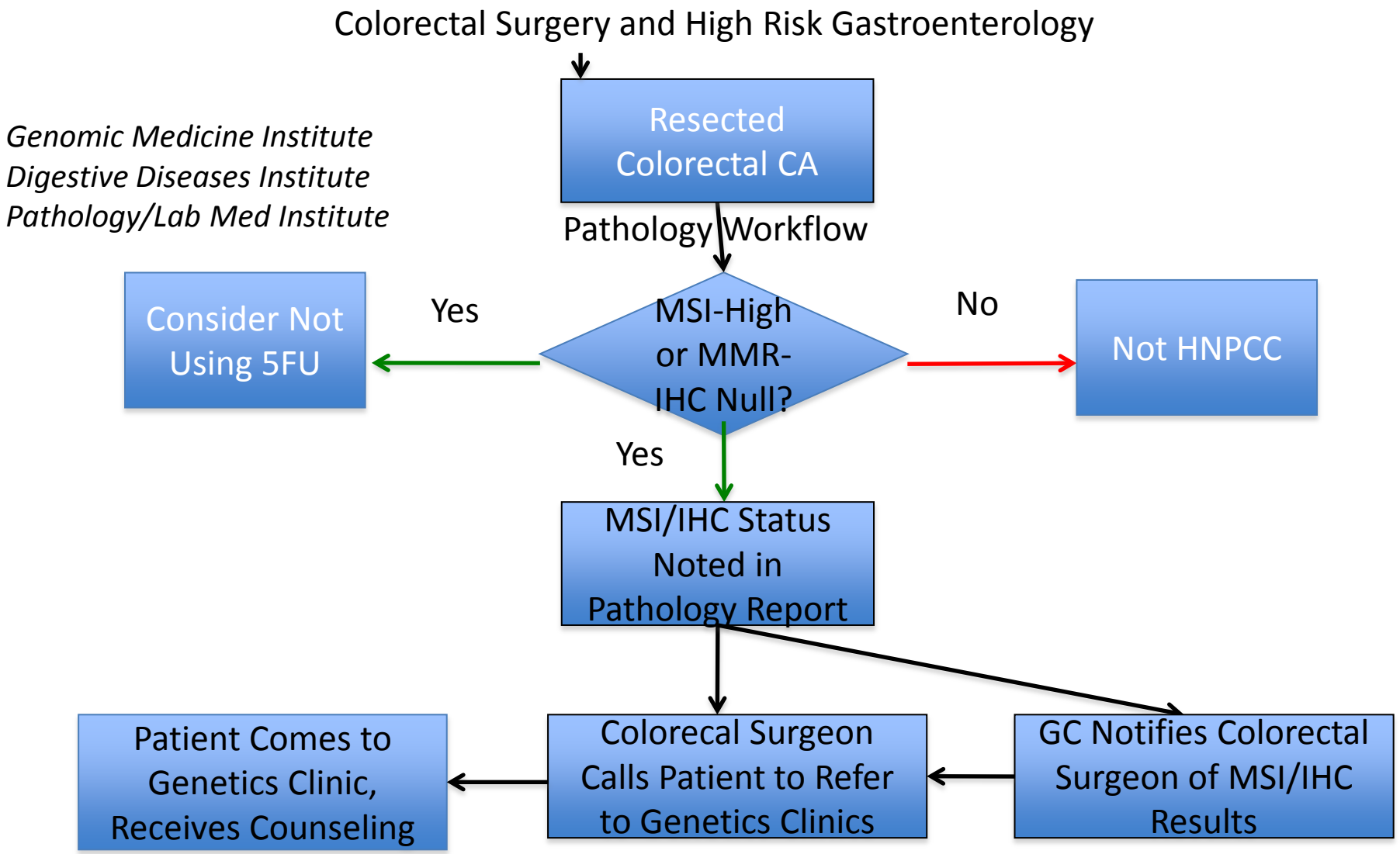
Genomic Medicine Institute
Digestive Diseases Institute
Pathology/Lab Med Institute

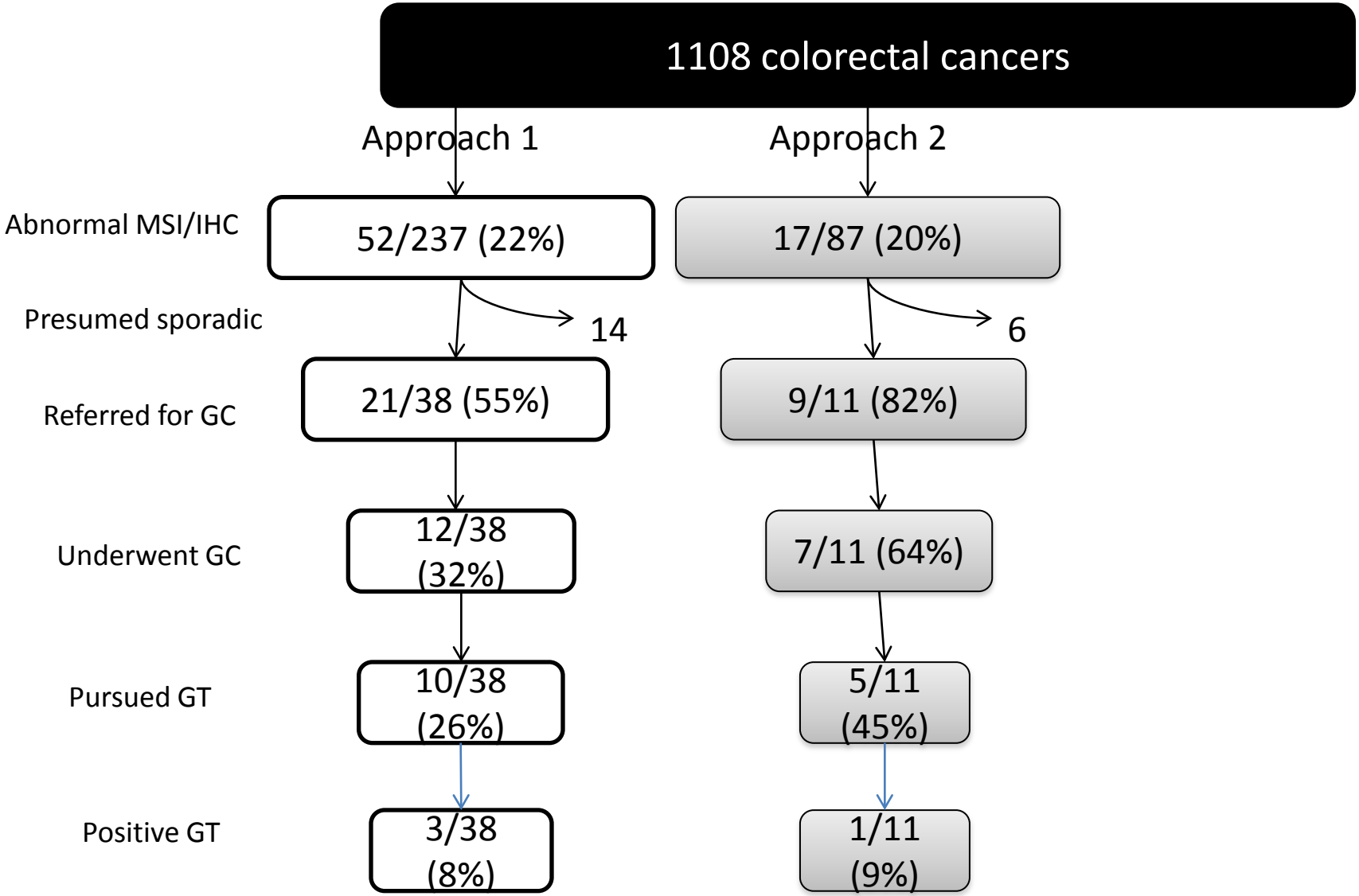


GC = Genetic Counseling
GT = Genetic Testing

Heald et al. *J Clin Oncol*, in press

Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2007.8-2008.7) = Approach 2





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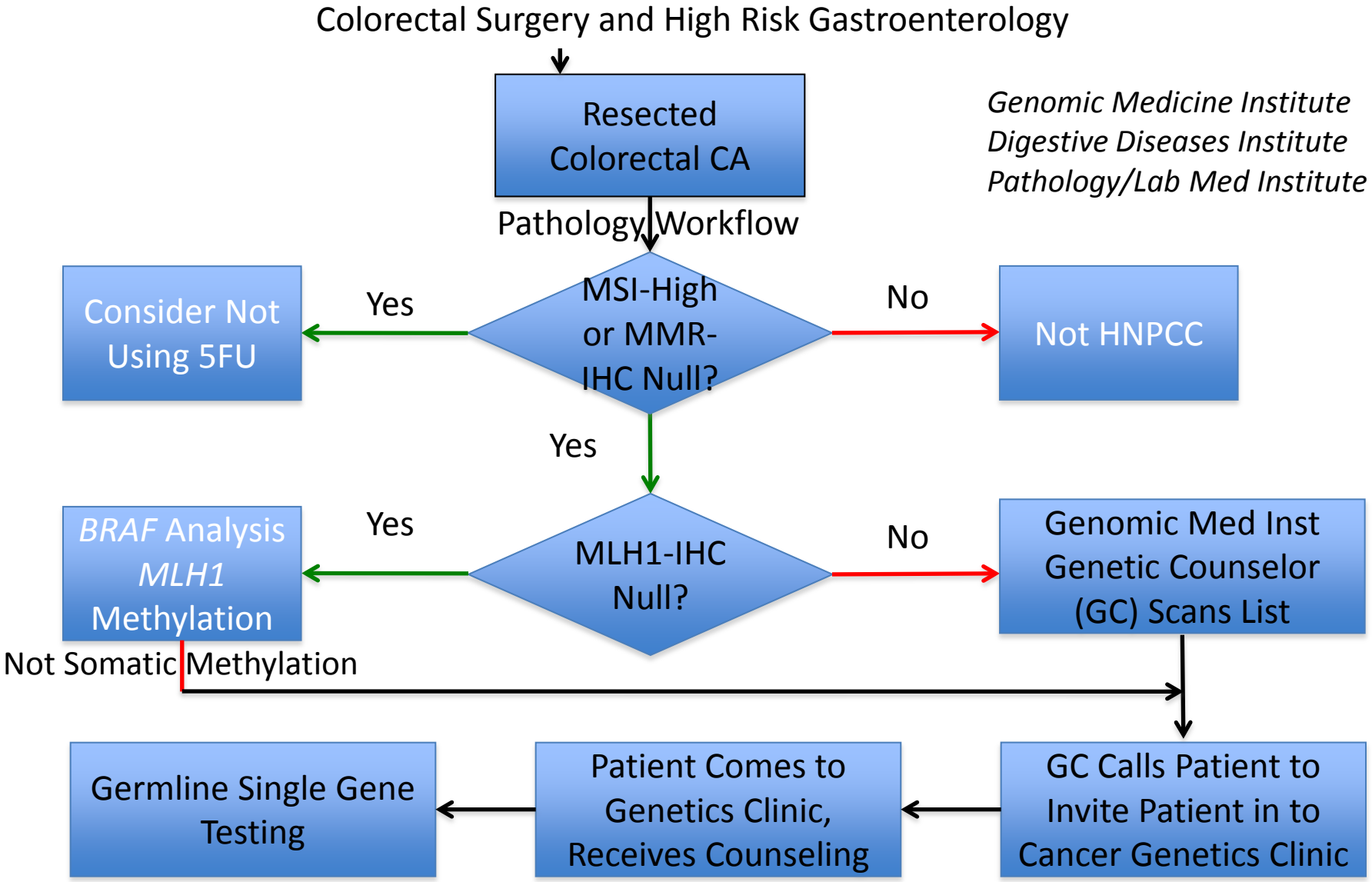
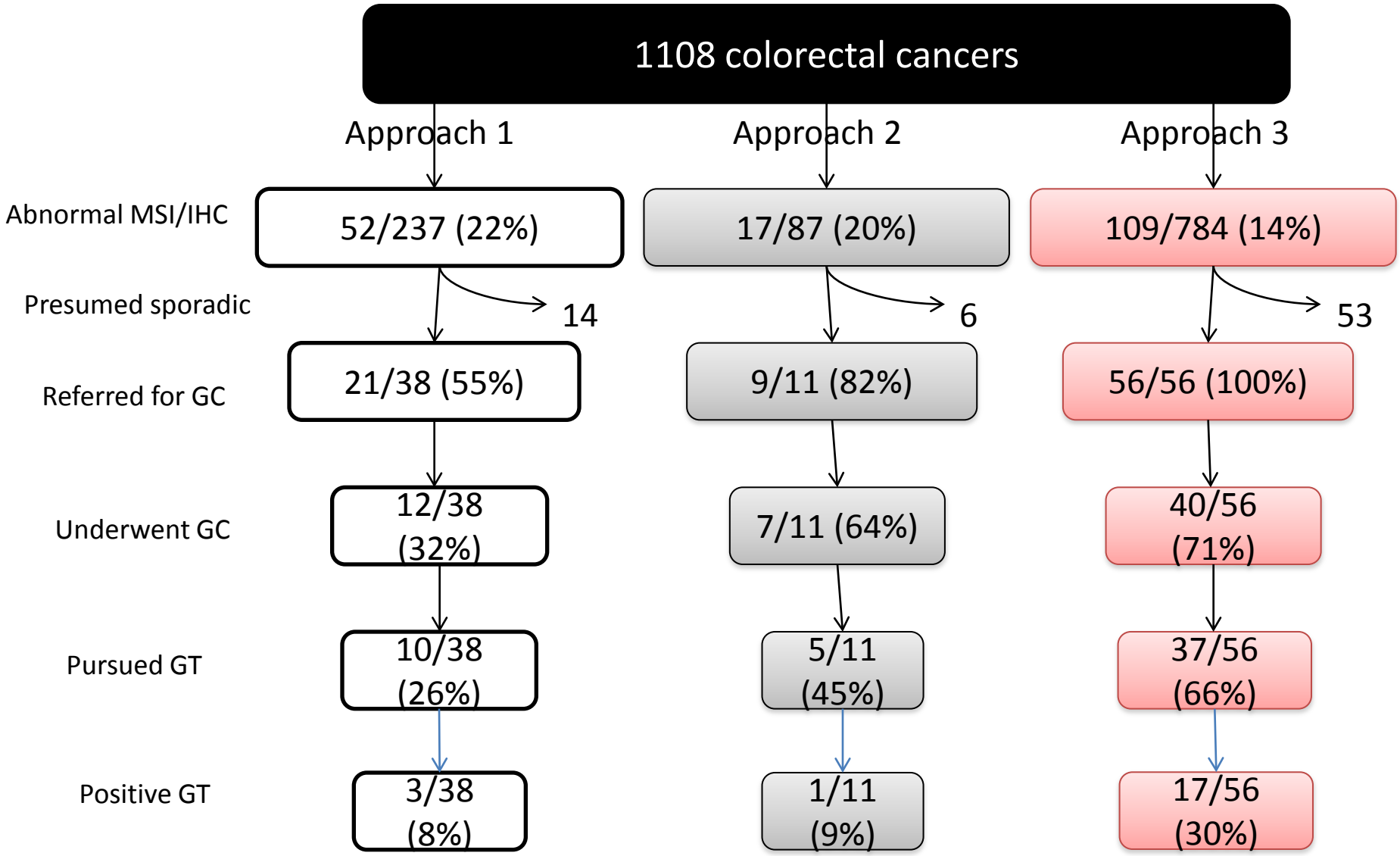
Heald et al. *J Clin Oncol*, in press

Cleveland Clinic Clinical Workflow for Screening All CRC for Lynch Syndrome (2008.7-onwards) = Approach 3





GC = Genetic Counseling
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Heald et al. *J Clin Oncol*, in press

Penn Med Update (and Challenges) on Adopting Universal Lynch Screening

- [In Process ….]

Quickie Reminder re Importance of Spotting Heritable Pheochromocytoma & Paraganglioma

- PCC/PGL Uncommon Neuroendocrine Tumours (NET)
- Can be Malignant or Not
- Can be in Inconvenient (Organ-Threatening) Spots
- Hormonally Active Ones -> Sudden Death, Hypertension, Stroke, etc
- 30-40% of All Comers Germline Mutations in ~10 Known Genes
- Gene-Specific Risks and Management
- Genotype-Clinical Outcome Association
- Actionable
- No Practice Guidelines

Out of GMII and III Came: "Systematic EMR-based ascertainment, genomic screening and clinical management of PC/PGL"

- *Four Primary Health Systems*:
- Cleveland Clinic Health System
  - Charis Eng, MD, PhD
  - Clinical Cancer Geneticist and Medical Oncologist
  - Co-Leader, European-American PC/PGL Registry and Work Group
- Medical College of Wisconsin
  - David Dimmock, MD
  - Clinical Geneticist
- Northwestern University Health System
  - Peter Kopp, MD, PhD
  - Endocrinologist
- University of Pennsylvania Health System
  - Katherine L. Nathanson, MD
  - Internist and Medical Geneticist
  - Director, PennNET
  - Co-Chair, TCGA PC/PGL Project

Objectives

- **Aim 1: To develop a systematic approach for ascertaining all PC and PGL patients for clinical genetics evaluation**
  - Construct and implement an EMR alert to remind clinicians that referral to genetics is indicated
  - Measure improvements in ascertainment/referral using EMR searches
  - Provide genetics education and clinical decision support for physicians involved in the care of PC and PGL patients
  - Query pathology and billing reports for PC/PGL on a regular basis for quality control

- **Aim 2: To determine the most impactful genetic testing strategy for the patient with an apparently non-syndromic high-risk PC/PGL**
  - Track yield (frequency of finding mutation) and costs for patients tested with traditional single-gene, tiered genetic testing versus whole exome sequencing
  - Compare effectiveness of single-gene tiered testing with panels
  - Offer whole exome sequencing to high-risk patients with negative testing
  - Track psychosocial impact between traditional testing versus exome approaches using MICRA

Objectives (Cont'd)

- **Aim 3: To measure impact of gene testing process and recommended follow-up and surveillance for gene positive and familial patients**
  - Track patient compliance with screening recommendations
  - Record incident new neoplasias and size during screening of mutation positive individuals
  - Model cost-effectiveness of traditional genetic testing process compared to exome approach
  - Define screening recommendations for Hereditary PC/PGL syndrome patients, so that we may use this study to create standard of care guidelines (ASCO, ACMG) for patients with Hereditary Paraganglioma-Pheochromocytoma Syndrome
- Submitted to U01 GM Pilot Demonstration Projects RFA

Three-Year Experience with Web-Based Patient-Entered Cancer Family History Prototype Tool

- Cancer Family History Prototype Tool (MyFHH)
- Cleveland Clinic Oncology-Focused Clinical Settings
- Scheduling Qualifying Appointment Triggers Invite to Patient to Complete MyFHH at Secure Portal
- MyFHH is a Cleveland Clinic Quality Improvement Initiative
  - To improve the efficacy of taking cancer family history assessment
  - Without introducing care disparity
- Analyzed Uptake of MyFHH by:
  - Personal diagnosis of neoplasm
  - Sex
  - Age
  - Socioeconomic status (SES)

Doerr and Eng, unpublished

Hypotheses

- Uptake of MyFHH Higher for Individuals with Personal Neoplasia History
- Uptake of MyFHH Higher for <65 y/o
- Uptake of MyFHH Higher for Higher SES

Sept 2009-Aug 2012: 1161 Patients Scheduled Qualifying Appointments with Invite to Enter MyFHH

- Personal History of Neoplasia: 877 (76%)
- Female: 1002 (84%)
- Age <65: 994 (87%)
- SES Estimated by Median Family Income by Zip Census Tabulation Area

Doerr and Eng, unpublished

Odds of Completing MyFHH (Univariate Analysis)

- NO Difference in Odds of Completing MyFHH:
  - Personal Diagnosis of Neoplasm
  - Sex (Trend for Men Not Completing)
  - SES
- Decreased Odds of Completing MyFHH for Those >65 yo
  - OR 0.47; 95%CI 0.31, 0.71; P<0.001
  - Multivariate Analysis (Adjusted for Personal Dx, Sex, SES) OR 0.48; 95%CI 0.32, 0.72; P<0.001

Doerr and Eng, unpublished

Next Steps

- Focus Group and Survey for Barriers of >65 YO Participants
- Focus Groups and Survey to Determine Shared Domains Across All Ages Correlating with Uptake
- MyFamily: Scalable Family Health History Tool:
  - Web-Based, Patient-Entered Family History and Clinical Decision Support Platform at the Point of Care
  - Automated Risk Assessment by Modules, examples include:
    - General Cancers
    - Hereditary Breast-Ovarian Cancer Syndrome
    - Lynch Syndrome
    - Abdominal Aortic Aneurysm
    - Diabetes Mellitus
  - EMR-Compatible
- MyFamily Currently Beta-Testing in 5 Diverse Clinical Settings Across Cleveland Clinic Health System (Sept., 2012 ff)
  - Beta Test Data to be Analyzed Q1-2, 2013
- Will Need to Beta-Test with Clinical Settings Distinct from Cleveland Clinic