Whole Genome Sequencing at The Partners HealthCare System (PHS)

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BRIGHAM AND WOMEN'S HOSPITAL

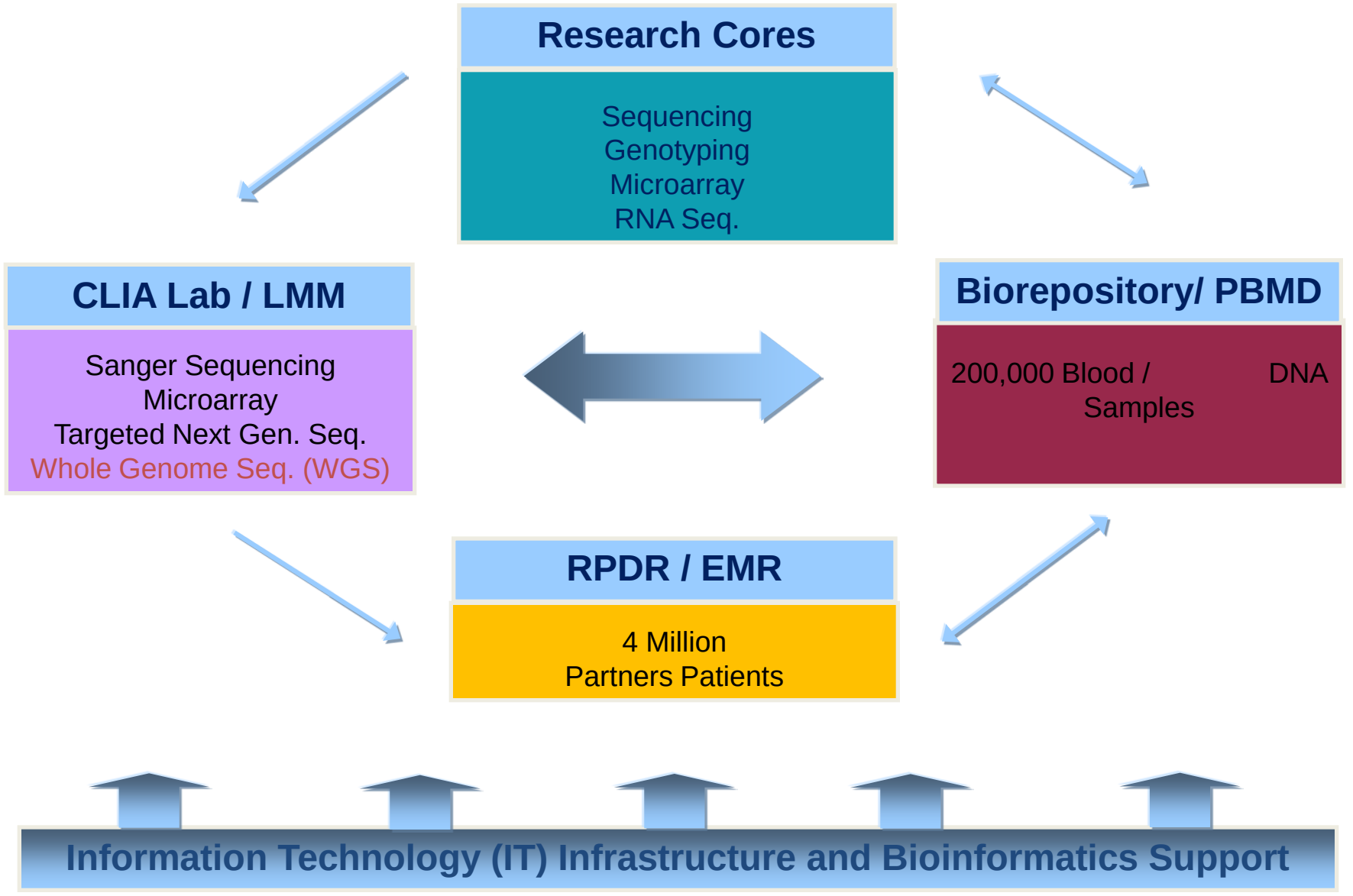
MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Outline

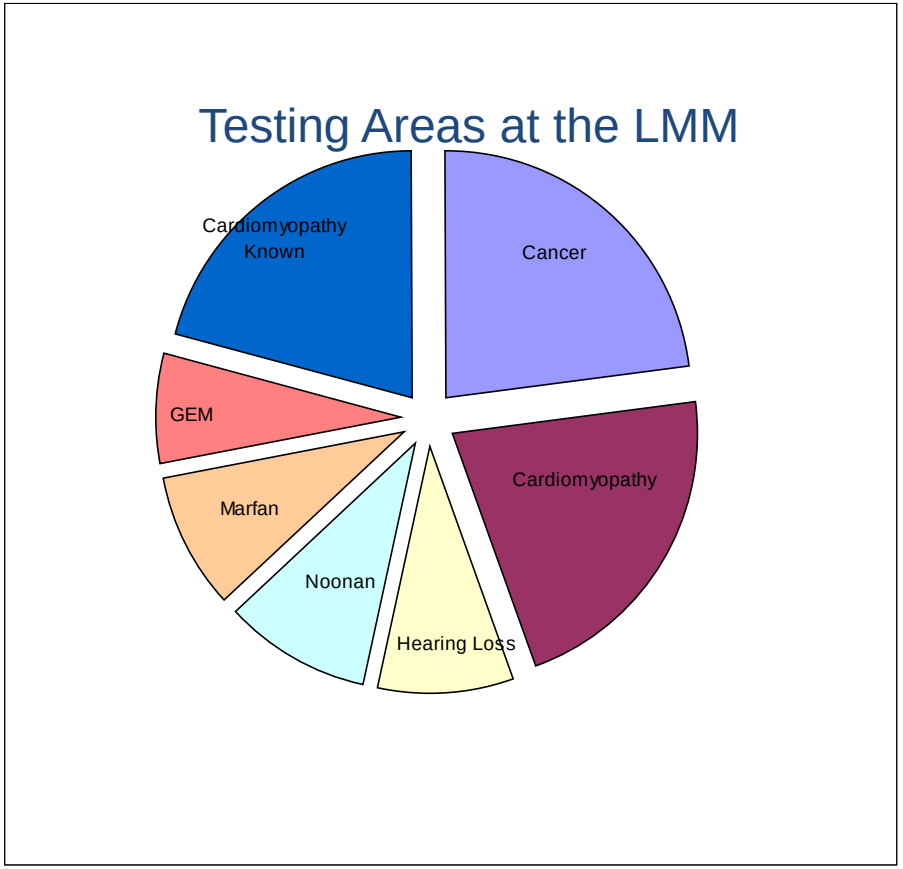
- Components of the Partners Center For Personalized Genetic Medicine
- Laboratory for Molecular Medicine (LMM)
- Whole Genome Sequencing for clinical use
- GeneInsight Lab and Clinic
- Acknowledgements

How PCPGM Components Links to Each One



Laboratory for Molecular Medicine (LMM)

- CLIA certified lab licensed through Massachusetts General Hospital, opened in Nov 2003
- Offers high complexity Genetic tests (LDTs – laboratory developed tests)
  - Exempt from FDA approval but require validation of performance characteristics by the lab
  - Main testing platforms are capillary and array-based sequencing
  - Launched Next Gen Sequencing Tests for Cardiomyopathy in July 2011
  - 200 genes, >4000 tests/year



Predicting Treatment Response Lung Cancer

May 20/June 4, 2004

The NEW ENGLAND JOURNAL of MEDICINE

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Study by Massachusetts General Hospital

Science

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

Study by Dana Farber Cancer Institute

3 Months

Science, August 27, 2004

Test available to patients

PHARMACOGENOMICS

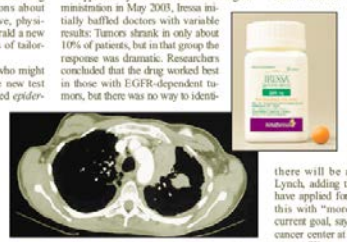
Cancer Sharpshooters Rely on DNA Tests for a Better Aim

Without fanfare, two diagnostic labs have launched a genetic test to guide doctors treating a common and deadly form of lung cancer. Despite lingering questions about whether the test is comprehensive, physicians think this approach could herald a new generation of gene-based methods of tailoring cancer treatment.

Designed to pinpoint patients who might be helped by the drug Iressa, the new test hunts for mutations in a gene called *epidermal growth factor receptor* (*EGFR*), whose protein Iressa targets. People who test positive may be more likely to benefit from this therapy, which has an impressive record in treating non–small cell lung cancer—but only in a small fraction of cases. If screening takes off, it could significantly affect the roughly 140,000 U.S. patients diagnosed each year with this type of cancer.

This month, a Harvard-affiliated diagnostics lab rolled out its version of the Iressa test, following a similar decision in July by the City of Hope hospital in Duarte, California. Both offer similar tests to lung cancer patients (at a cost of $500 to $2000), screening for mutations in DNA isolated from tumors.

Approved by the U.S. Food and Drug Administration in May 2003, Iressa initially baffled doctors with variable results: Tumors shrank in only about 10% of patients, but in that group the response was dramatic. Researchers concluded that the drug worked best in those with EGFR-dependent tumors, but there was no way to identify such patients. That became possible last spring, when two independent teams of scientists at Massachusetts General Hospital (MGH) and the Dana-Farber Cancer Institute, both in Boston, reported that Iressa responders have mutations in a specific stretch of the *EGFR* gene (*Science*, 30 April, p. 658).



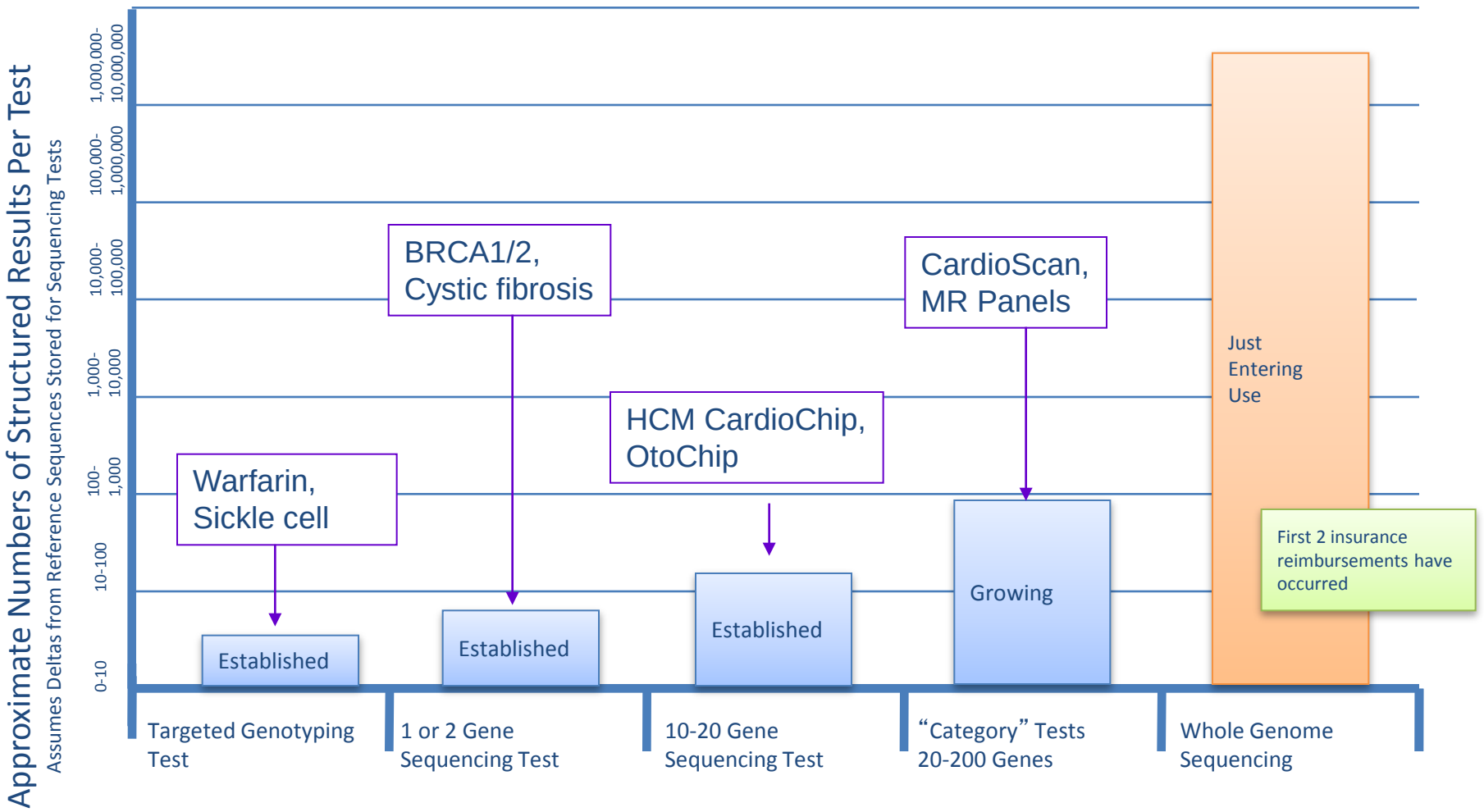
Genetic forecasting. Doctors hope a new gene test will help them pick and choose patients whose lung tumors (above, right) are most likely to shrink thanks to the targeted drug Iressa.

"Hundreds of patients have contacted us" to learn their *EGFR* status, says Thomas Lynch, who directs the center for thoracic oncology at the MGH cancer center and was a lead author on one of the spring papers. Adds Matthew Meyerson, a pathologist at Dana- Farber and an author of the second paper: "Our goal, basically, is to get the test into the widest and fastest possible use."

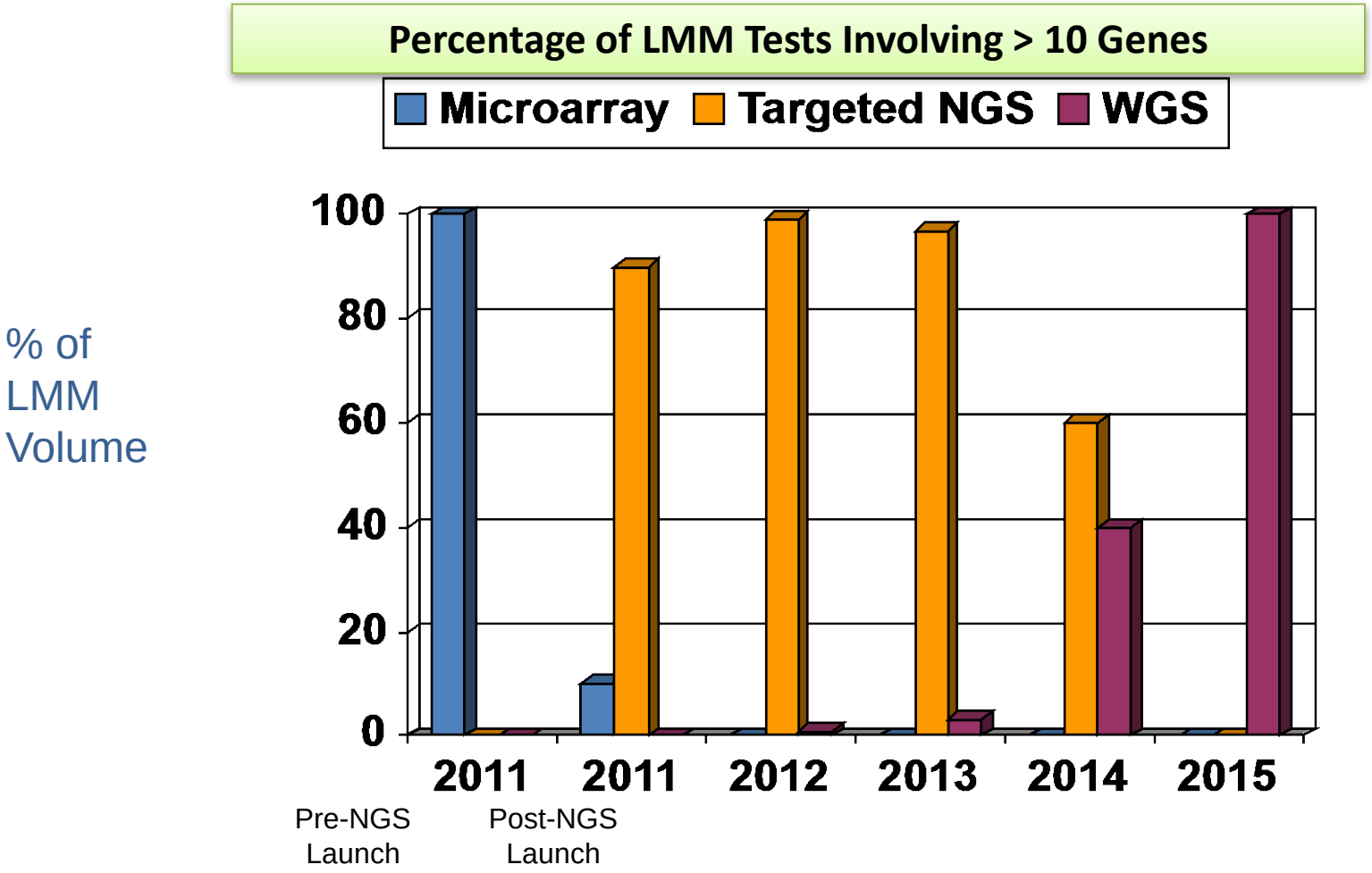
But the details must be ironed out. For one, the research groups are not equipped to handle the hundreds of thousands of samples that could flood in. (So far, each has tested fewer than 20.) "We're hoping there will be a commercial test," says Lynch, adding that MGH and Dana-Farber have applied for patents and are discussing this with "more than one company." The current goal, says Daniel Haber, head of the cancer center at MGH, is to sign on a company willing to distribute the genetic test to hospitals that want to screen their own patients. "We are not looking at the model Myriad has," he says, referring to Myriad Genetics, the Salt Lake City, Utah, company whose monopoly over two breast cancer gene tests has spurred controversy.

Discovery → Merge Molecular, Clinical Data → Clinical Validation → **Patient**

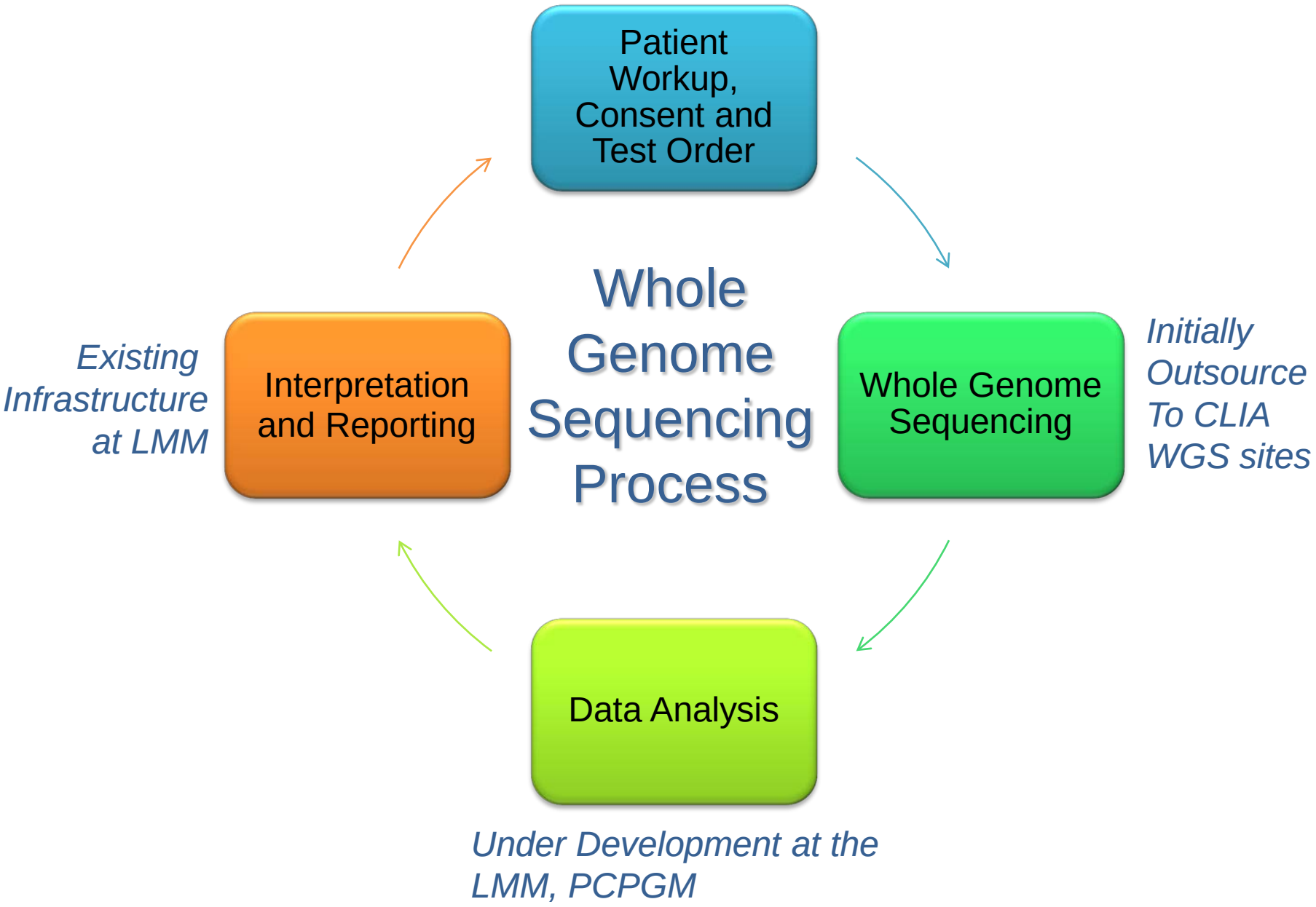
Context: Evolution of Clinical Genetic Testing



We Anticipate WGS Will Render Targeted NGS Obsolete In About 4 Years



BWH and MGH Clinics

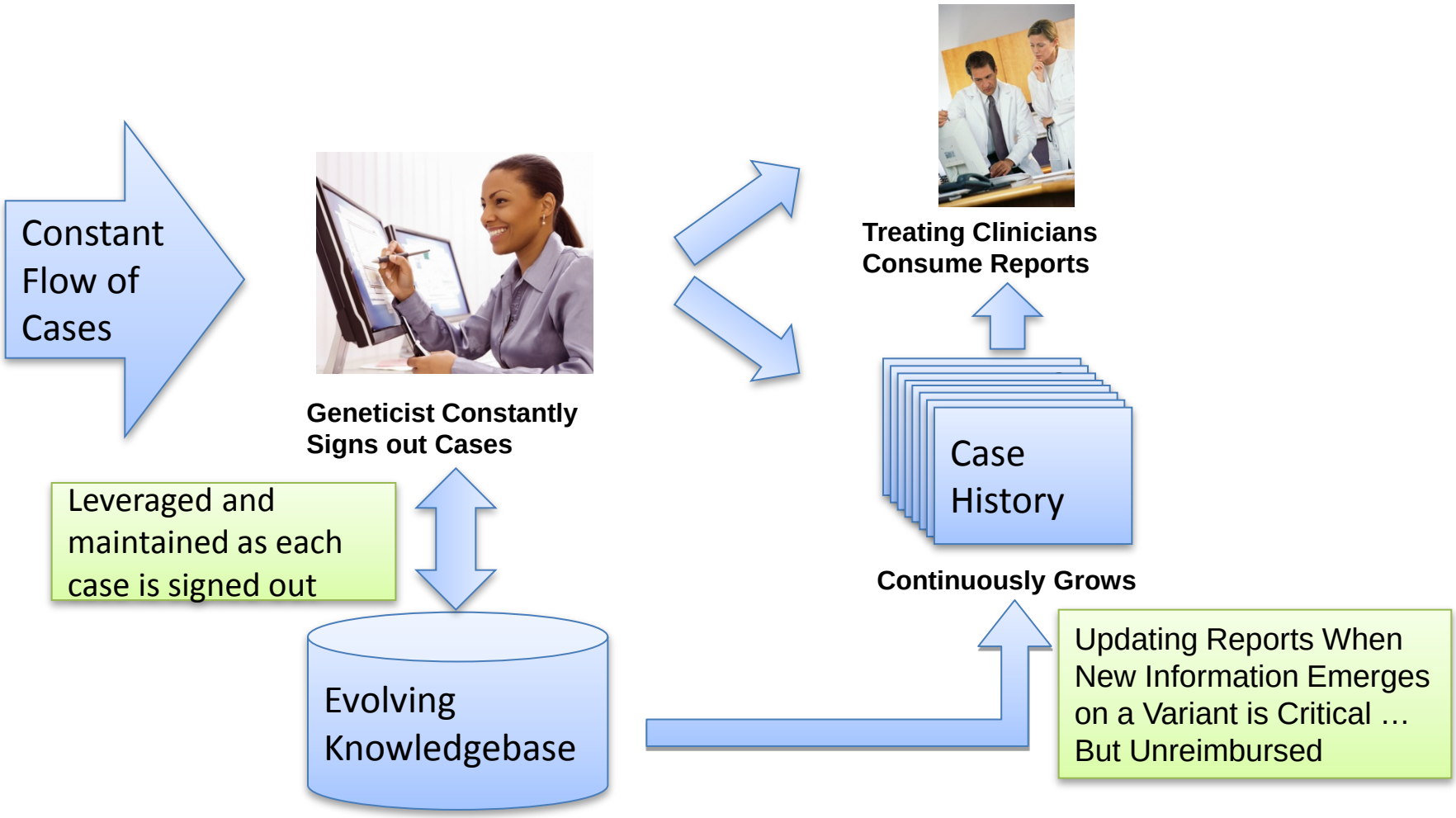


Context: The Clinician's Perspective

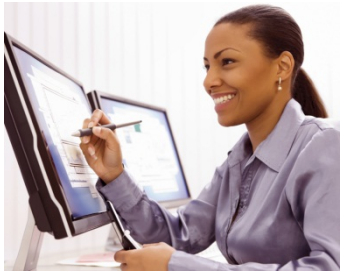
- Whole genome sequencing will generate 2-5 million variants per patient tested
- New information can emerge on any variant at any time
- New forms of support are already needed to stay up to date on the limited number of variants identified by today's category tests
- Infrastructure dependent clinical processes need to be established to:
  - Enable clinicians to receive and manage genetic results
  - Link clinicians to experts capable of determining the implications of each patient's genetic profile
  - Keep the up to date

This Creates Significant Opportunities
Along Multiple Dimensions for PHS

A Key Challenge in Personalized Medicine



Driving Cost Out of the System



Geneticist Constantly Signs out Cases

Treating Clinician Consumes Reports

Case History

Continuously Grows

New Variant Assessments and Knowledge Base Updates

Reports

Cases / Identified Variants

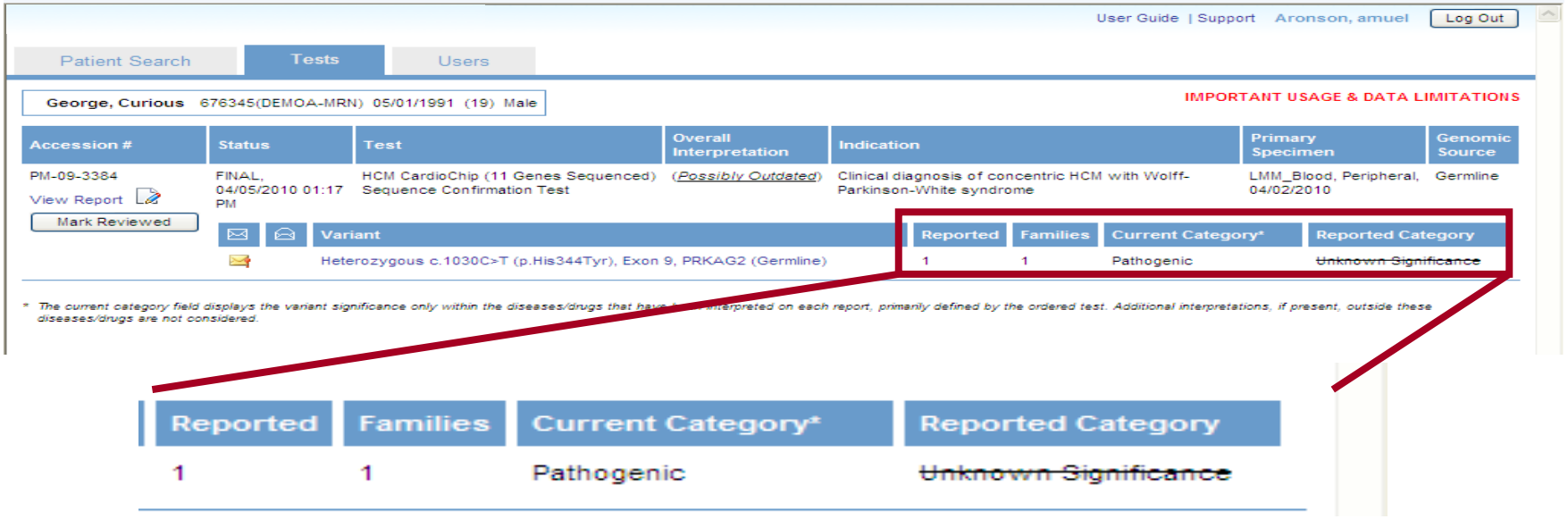
GeneInsight

Report Generation Engine

Knowledgebase

Occurs Automatically on Knowledgebase Update
No Case Level Work Required

GeneInsight Clinic



- Enables management of patient genetic profiles
- Delivers alerts as new variant information emerges

Provides Direct and Indirect Links to Clinician Desktops
Thereby Creating a Very Powerful Distribution Channel

Acknowledgments

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