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Identifying Diabetes Subtypes: A Model for Genomic Medicine

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Molecular medicine comes to the rescue

Targeted therapy turns life around for child with neonatal diabetes

On Monday, August 14, Lilly Jaffe, a six-year-old North Shore suburban girl who had been diagnosed with type 1 diabetes when she was one month old, checked into the Clinical Research Center at the University of Chicago Medical Center. On Friday, August 18, she checked out, starting to make her own insulin, well on her way to insulin independence and ready to get in a few days of beach time in Michigan before starting first grade.

http://www.uchospitals.edu/news/2006/20060911-diabetes.html

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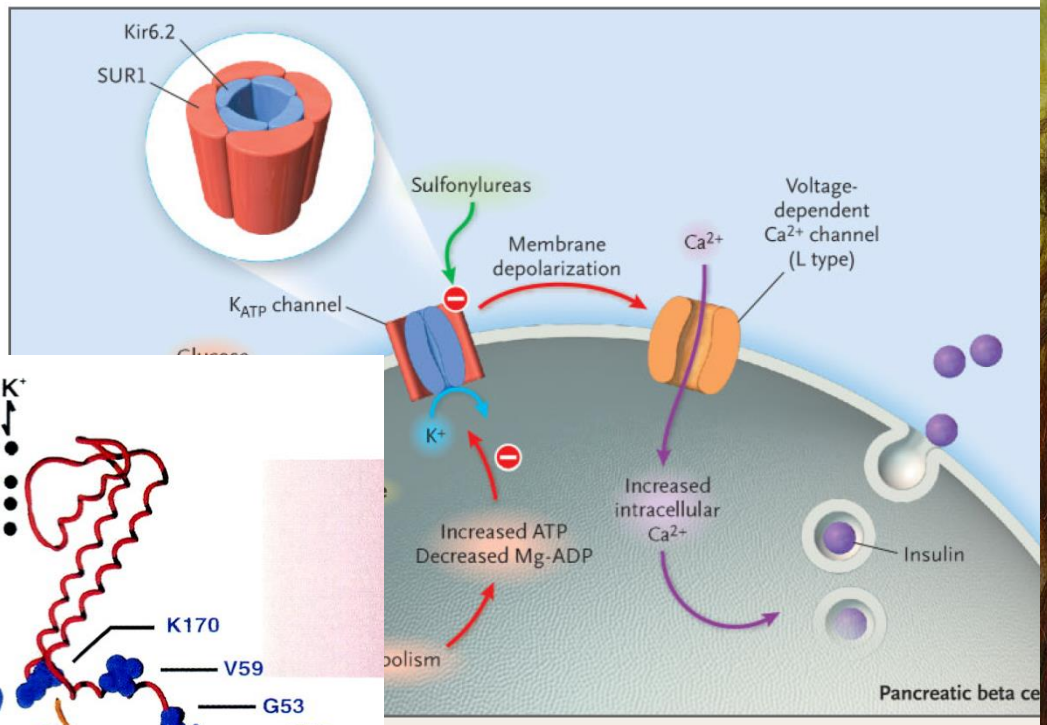
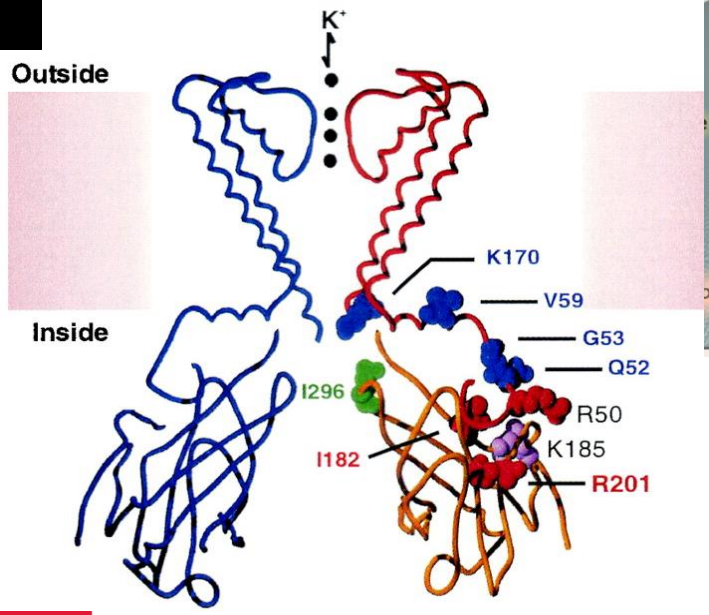
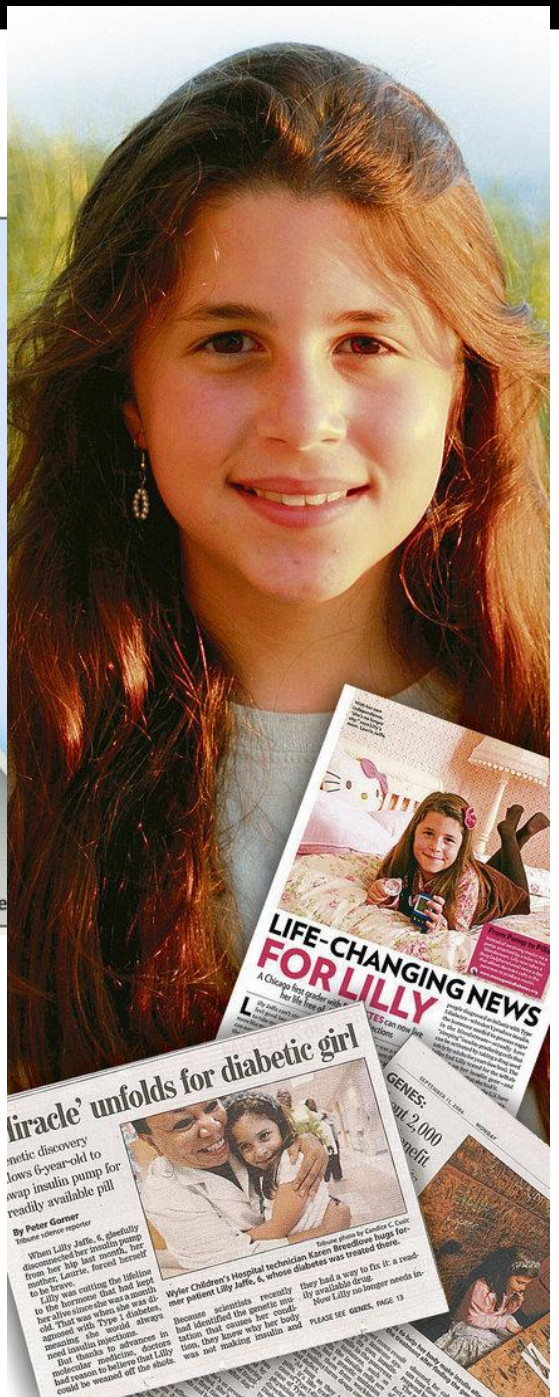
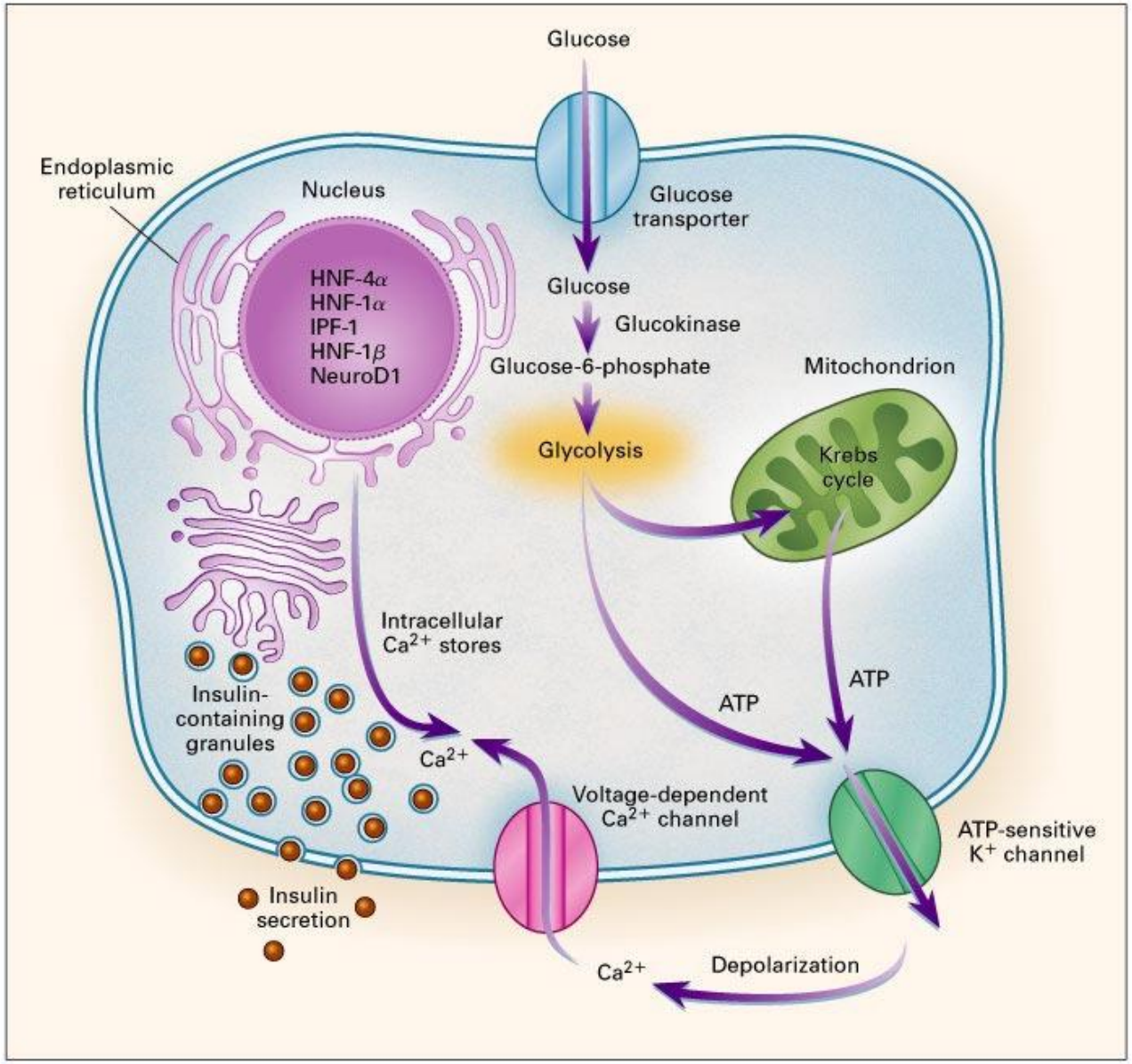


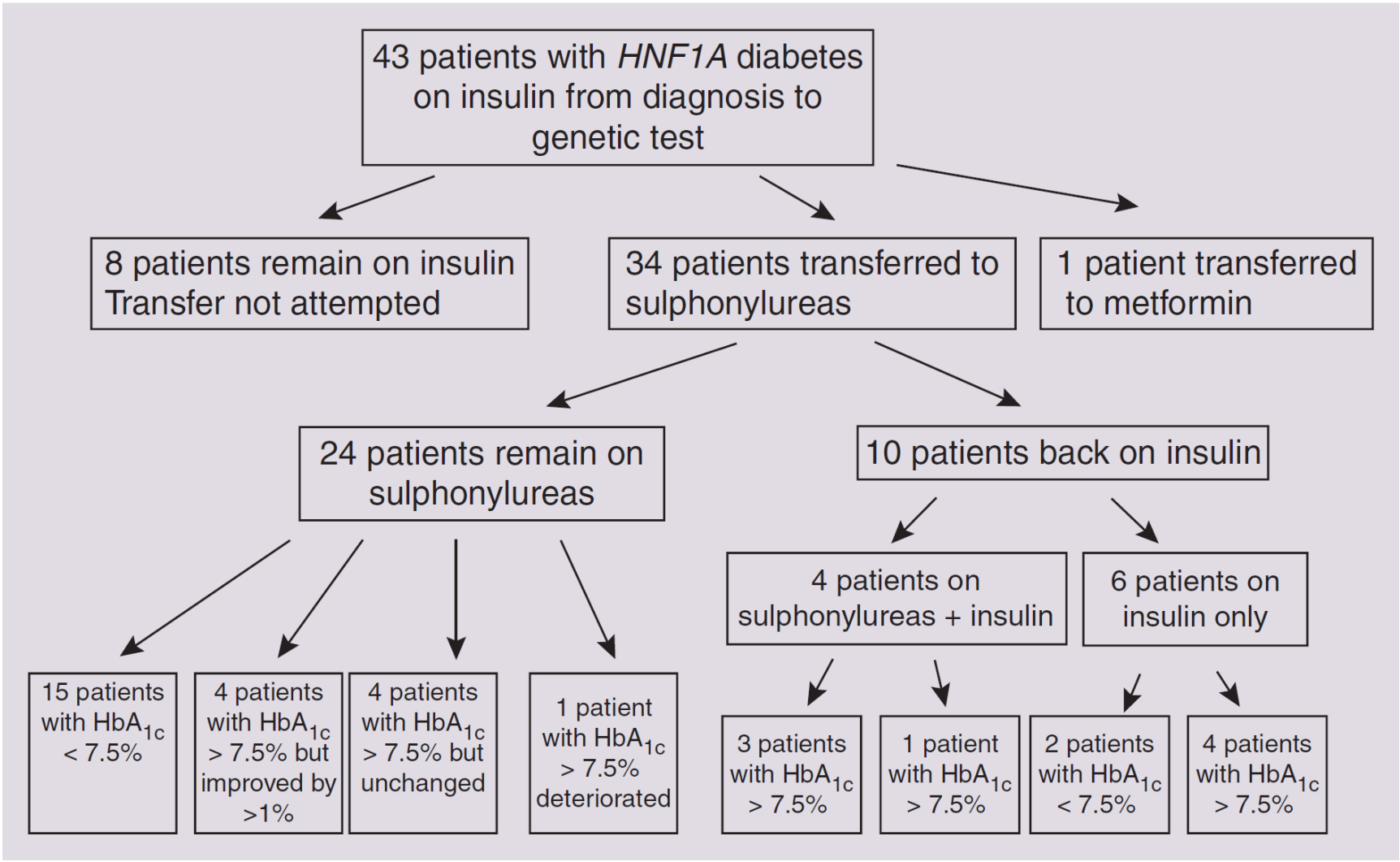




NEJM 350:1838-49, 2004
Diabetes 54:3065-72, 2005



Fajans et al, *NEJM* 2001



Shephard et al, *Diabetic Medicine* 2009

FORUM

'I don't feel like a diabetic any more': the impact of stopping insulin in patients with maturity onset diabetes of the young following genetic testing

Maggie Shepherd and Andrew T Hattersley

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Clin Med 2004;4:144–7

ABSTRACT – Hepatocyte nuclear factor-1α (HNF-1α) maturity onset diabetes of the young (MODY) is the commonest cause of monogenic diabetes but is frequently misdiagnosed as type 1 diabetes. The availability of genetic testing in MODY has improved diagnosis. Sulphonylurea sensitivity in HNF-1α patients means that those on insulin from diagnosis can transfer to sulphonylureas and may improve glycaemic control. To gain insight into the implications for patients of stopping insulin, in-depth interviews were conducted with eight HNF-1α patients transferred to sulphonylureas after a median of 20 years on insulin. Thematic content analysis highlighted four key themes:

- **fear, anxiety and excitement regarding stopping insulin, particularly among those who had been on insulin for many years or they no longer required injections as this conflicted with messages previously received from healthcare professionals.**

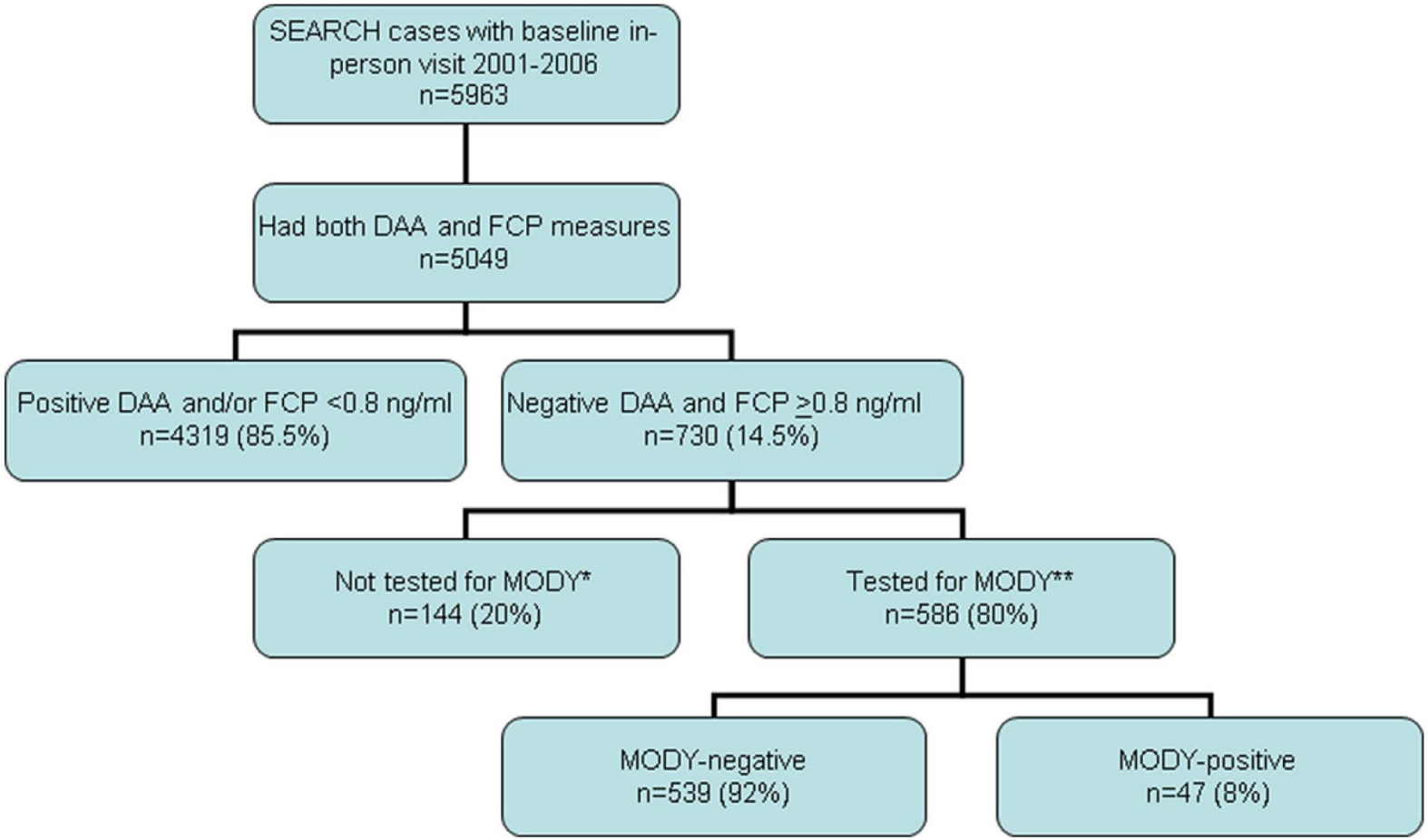
Transferring from insulin to sulphonylureas had a positive impact on lifestyle but support was needed for patients to adjust, many having grown up with the belief they would be on insulin for life.

KEY WORDS: genetic testing, hepatocyte nuclear factor-1α (HNF-1α), maturity onset diabetes of the young (MODY), sulphonylurea sensitivity

Background

Maturity onset diabetes of the young (MODY) is an unusual genetic type of diabetes affecting 20,000 people in the UK. It is characterised by a young age of

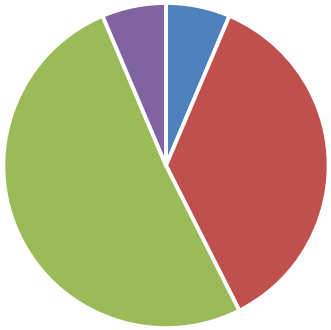
Monogenic Diabetes is Underdiagnosed: The SEARCH Study



Pihoker et al (2013), *JCEM* 98:4055

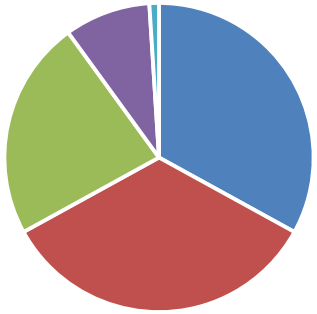
SEARCH Participants with MODY Mutations

Clinical Diagnosis

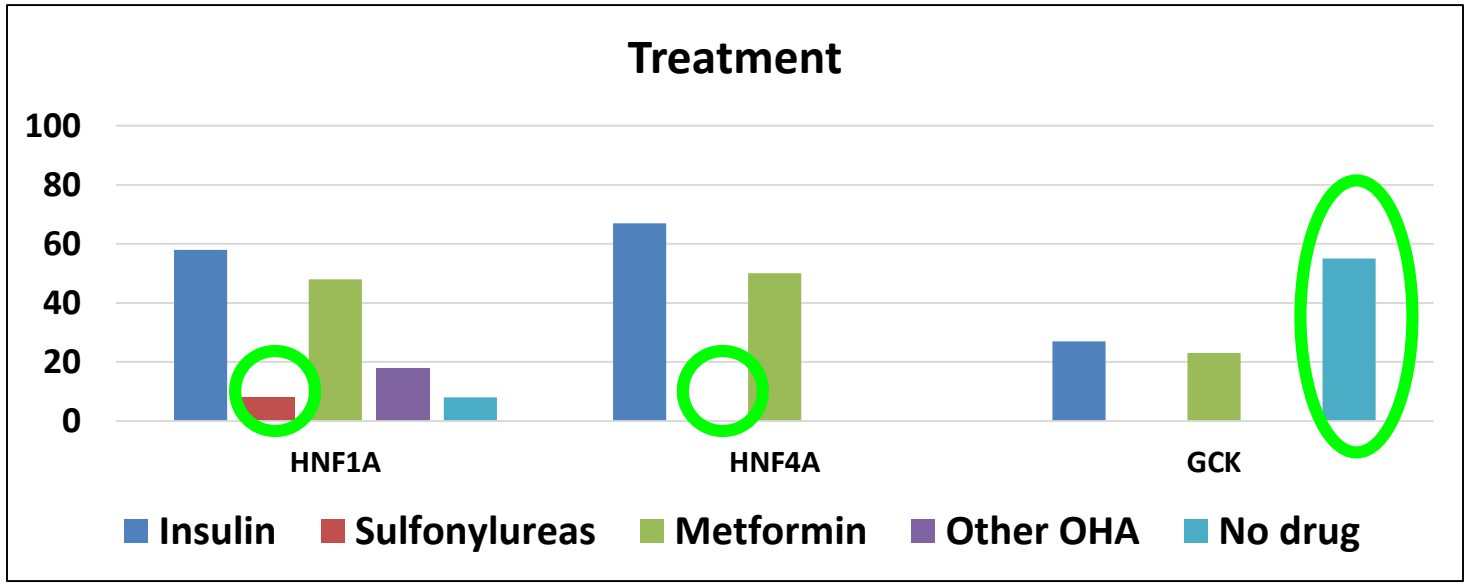


MODY T1DM T2DM Other

Ethnicity



NHWhite AA Hispanic Asian/Pac Other/Unk



Challenges

- Lack of provider/consumer/payer awareness
- Clinical overlap
- Notion that “rare means never”

- Life-changing vs. life-saving
- Expense/complexity of testing
- Limited professional society guidance

Components of the Personalized Diabetes Medicine Program

Patient completes questionnaire

- Diagnosed before 1 year?
- Diagnosed before 30 years?
- Age of diagnosis ____
- Hearing or visual impairment/birth defects/ kidney disease?
- Extremely overweight at diagnosis?
- Type 1 diabetes?
- Parent or child with type 1 diabetes?
- 2 or more people related by blood with diabetes?

Further workup as indicated

- C-peptide Positive?
- IA-2 Antibody negative?
- Consistent family/ medical history elicited by genetic counselor

If indicated…

- Sequence 40 monogenic diabetes genes for mutations

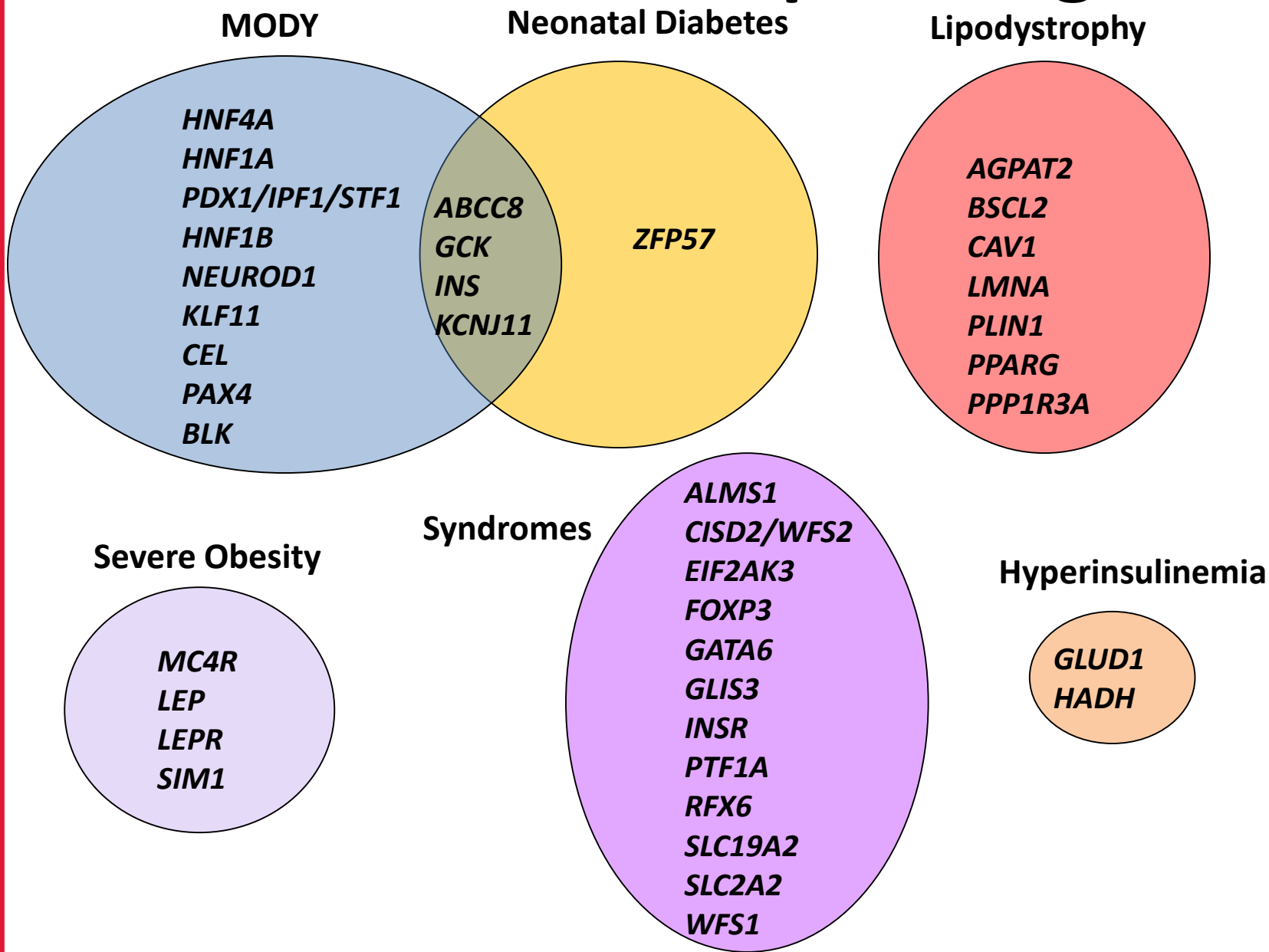
If pathogenic variant found:

- Confirm and add to electronic health record and customize treatment
- Make genetic counseling and testing available to family members

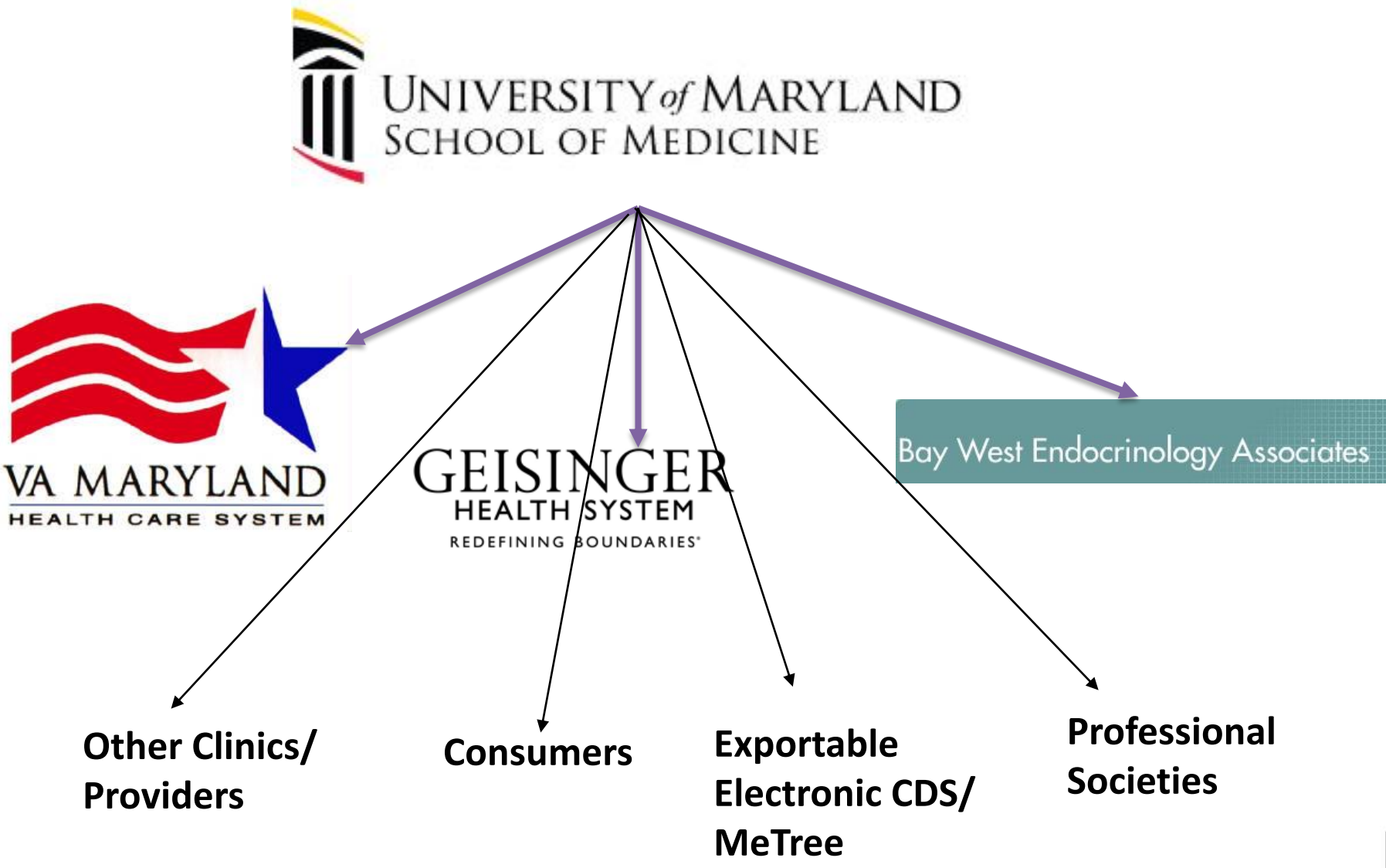
If variant of unknown Significance found:

- Segregation in family
- Functional studies

Next Generation Sequencing Panel



Dissemination of the PDMP

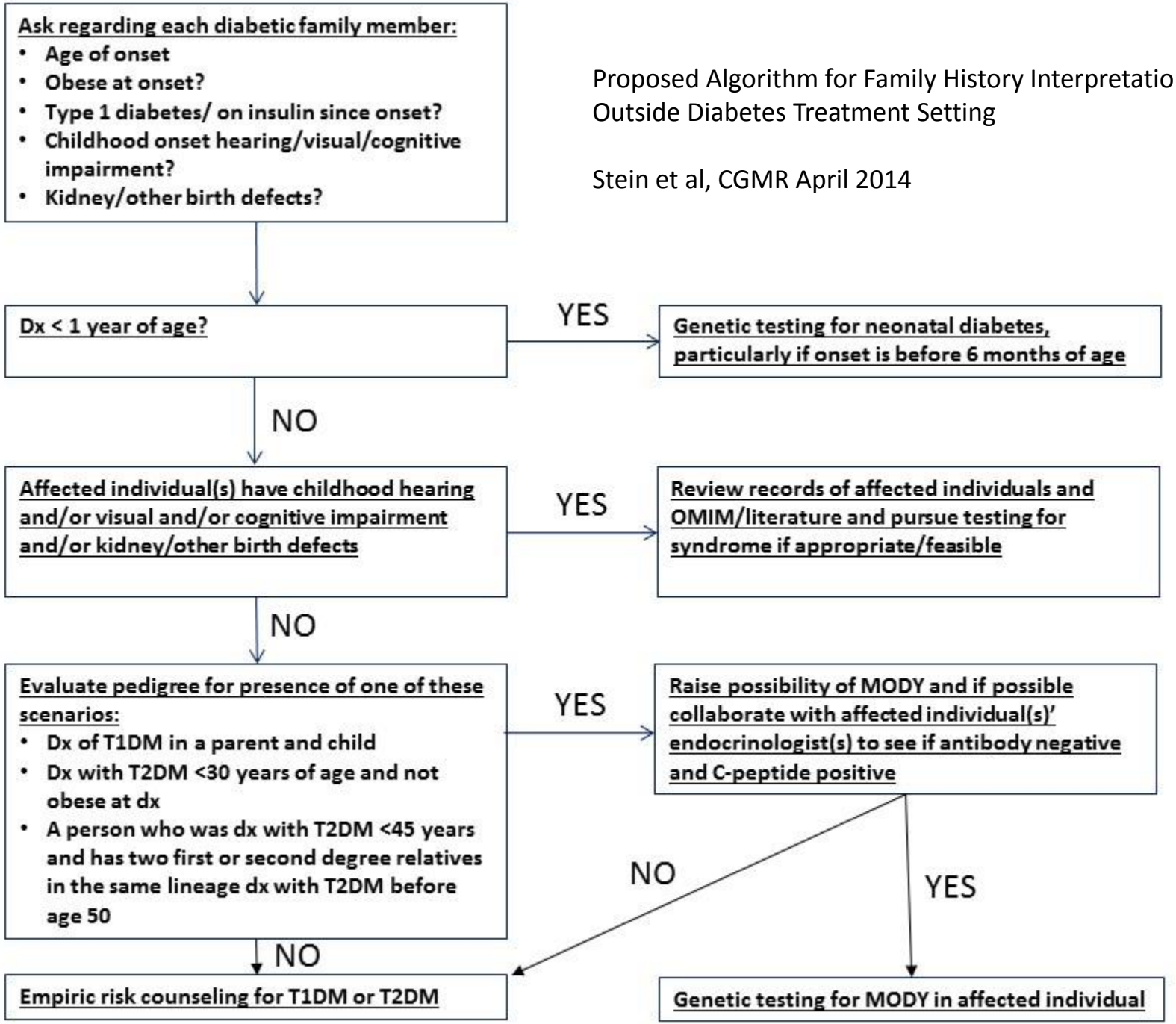


- **Aim 2: Conduct an impact evaluation** of implementation of systematic screening and molecular diagnosis and treatment of highly penetrant forms of diabetes on clinical and patient-reported outcomes, resource utilization, and barriers and facilitators of dissemination across diverse patient populations and healthcare delivery systems.

- **Aim 3: Engage a Payer Advisory Panel in the development of the impact evaluation process** to enhance our ability to collect meaningful evidence to inform clinical practice recommendations and guide insurance coverage decisions as a first step to enabling implementation of evidence-based PDMP to diagnose highly penetrant and inherited forms of diabetes across the United States.

Proposed Algorithm for Family History Interpretation Outside Diabetes Treatment Setting

Stein et al, CGMR April 2014



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- Kate Tracy
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- Stephanie Stein
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- Linda Jeng
- Coleen Damcott
- Nicholas Ambulos
- Jeff Kleinberger
- Trevor Matthias
- Danielle Sewell
- Keith Tanner
- Yue Guan
- UM CDE Staff and Patients

Program in Personalized and Genomic Medicine

GEISINGER HEALTH SYSTEM
REDEFINING BOUNDARIES

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genome.gov
National Human Genome Research Institute
National Institutes of Health

- NHGRI U01 HG00775

IGNITE Implementing GeNomics In practicE

- ignite-genomics.org

<u>Enrollment Information</u>

- http://umm.edu/programs/diabetes/research/clinical-trials
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