Diabetes Mellitus – A Model for Personalized Genetic Medicine

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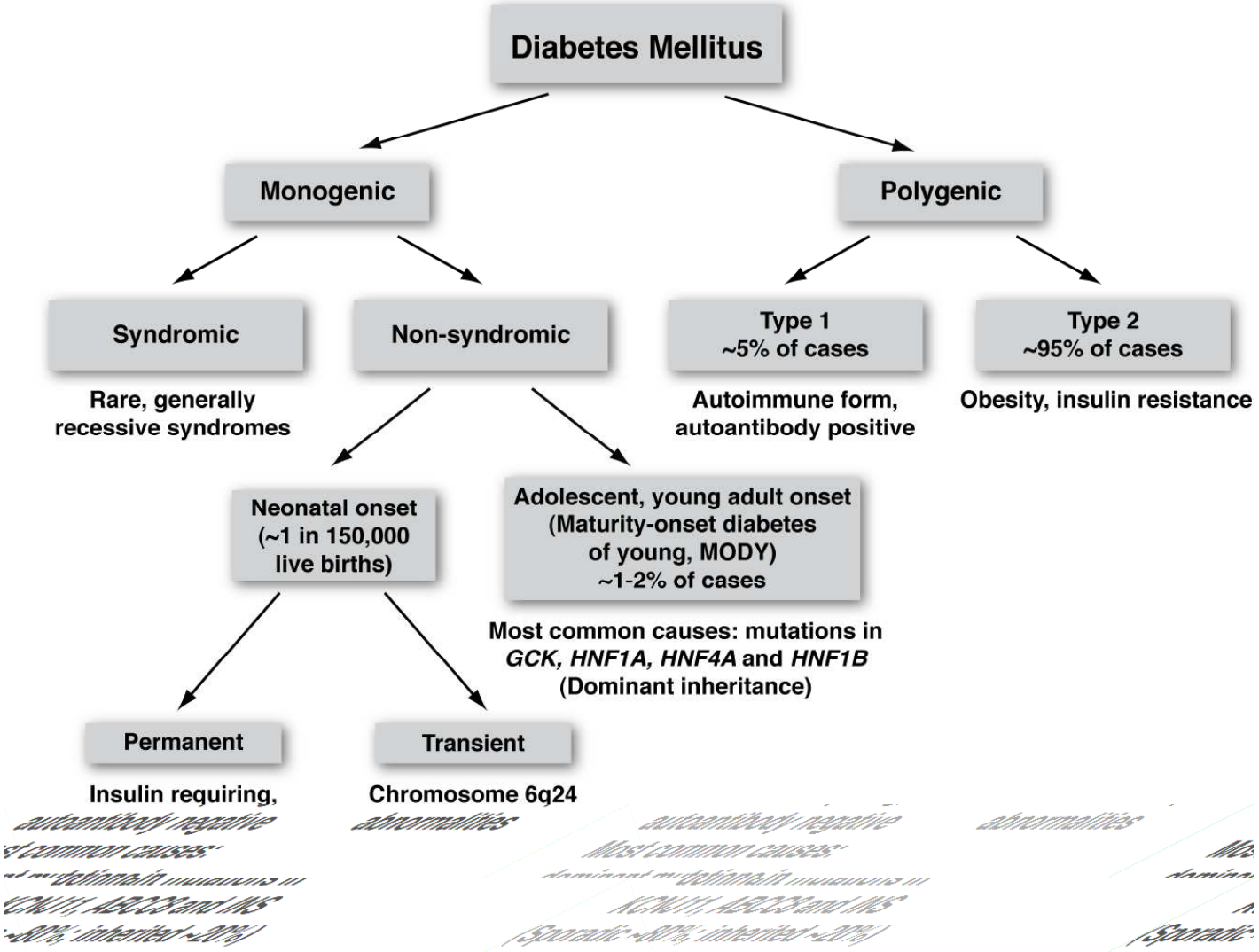
Etiologic Classification of Diabetes Mellitus: Not One Disease But Many

- Type 1 diabetes
  - Immune-mediated diabetes, β-cell destruction, absolute insulin deficiency; accounts for 5-10% of cases.
- Type 2 diabetes
  - Relative deficiency of insulin due to the inability of the β-cell to compensate for insulin demand due to obesity and other insulin resistant conditions; accounts for 90-95% of cases.
- Other specific types
  - *Genetic defects* (β-cell function and insulin action); *diseases of the exocrine pancreas* (e.g. cystic fibrosis); *endocrinopathies* (e.g. acromegaly, Cushing's syndrome); *drug- or chemical-induced*; *infections*; *uncommon forms of immune-mediated diabetes* (e.g. anti-insulin receptor antibodies); and other genetic syndromes sometimes associated with diabetes (e.g. Wolfram syndrome, Down syndrome)
- Gestational diabetes

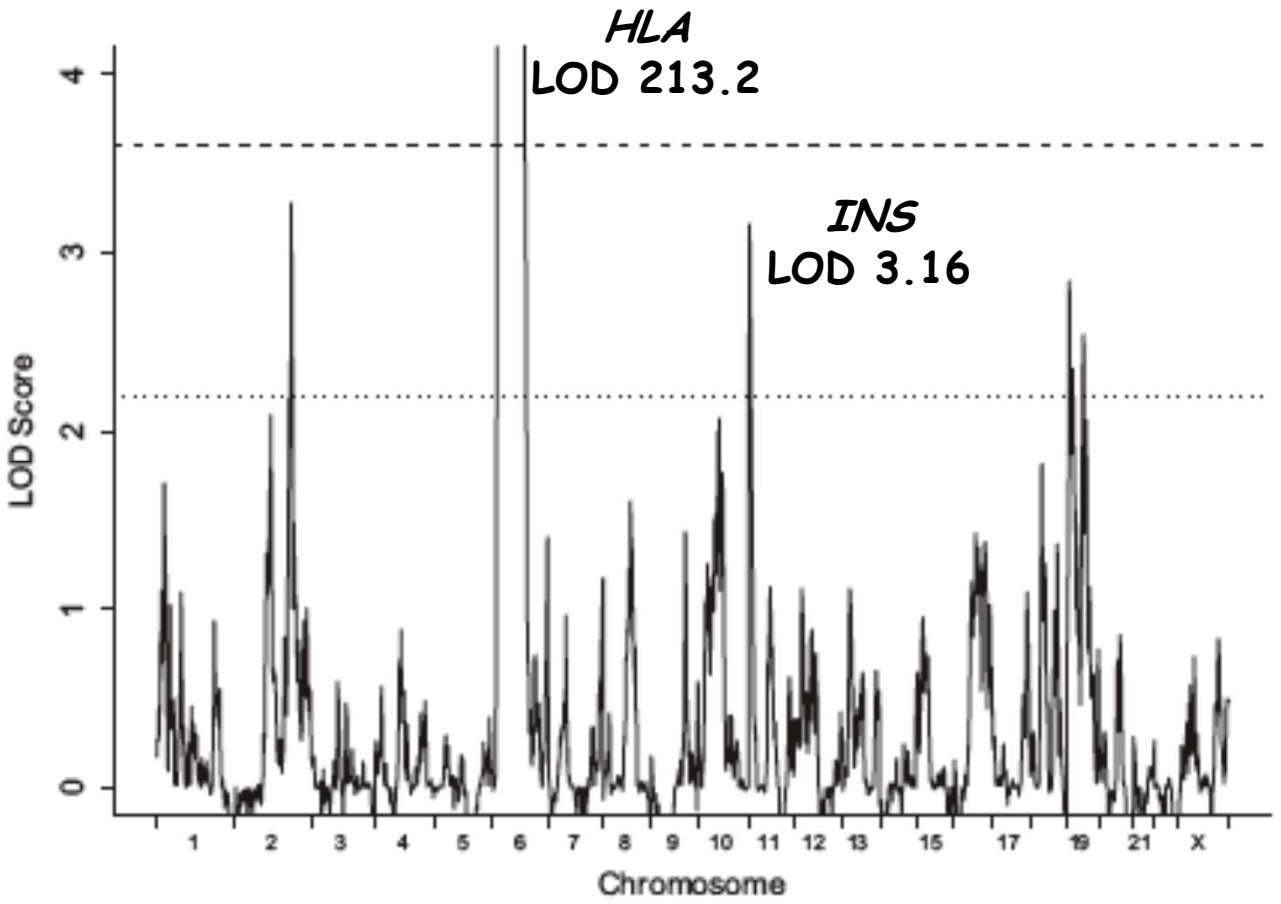
A Bell's-Eye View of Diabetes



Genetics of Type 1 Diabetes

A Polygenic Disorder or a Monogenic Disorder with Variable Penetrance?

Linkage Studies of Type 1 Diabetes (2,496 Multiplex Families)



Concannon et al., Diabetes 58:1018-1022, 2009

What Have We Learned from Genetic Studies of Type 1 Diabetes?

- Susceptibility determined by the effect of a major gene (or genes) in the HLA region of chromosome 6.
- Effect of HLA region gene(s) modified by at least 40 genes with only a small effect on risk - genetic background.
- Genetics alone are not useful in identifying those at risk of developing type 1 diabetes - presence of autoantibodies to beta-cell proteins may be more predictive.

Genetics of Type 2 Diabetes

A Very Polygenic Disorder

Linkage and Association Studies of Type 2 Diabetes

- Linkage studies have been carried out in many populations of all racial and ethnic groups and have revealed no major genes like HLA in T1D.
- Common variant genome-wide association and candidate gene studies have revealed about 70 loci to date that show genome-wide significant levels of association with T2D across multiple studies.

Genetic Studies of Type 2 Diabetes

- Effect sizes of T2D-associated genetic variants are small (OR: 1.1-1.4) and predictive value not greater than family history.
- Variants associated with T2D identified to date account for ~10% of the heritability of this disorder - the missing heritability!
- The genetic studies have implicated new loci in beta-cell function.
- A lot of biology remains to be done to understand how these new genes affect beta-cell function.

Genetic Studies of Type 1 and Type 2 Diabetes

- The linkage and association studies of type 1 and type 2 diabetes needed to be done to understand the role of genetics in their etiology.
- Will continuing genetic studies in larger and larger samples provide more insight into disease etiology?
- Why did the genetic studies work so much better in type 1 diabetes than type 2 diabetes?
  - Type 1 diabetes (at least type 1a) is a "single gene disorder of autoimmunity" with unknown environmental trigger.
  - Type 2 diabetes:
    - Not one disease but many and better phenotyping is needed to define subtypes. Studying individuals with the same phenotype (whatever that may be) may reveal genes with larger effect on risk;
    - Or Rare variants play a more important role than common variants.

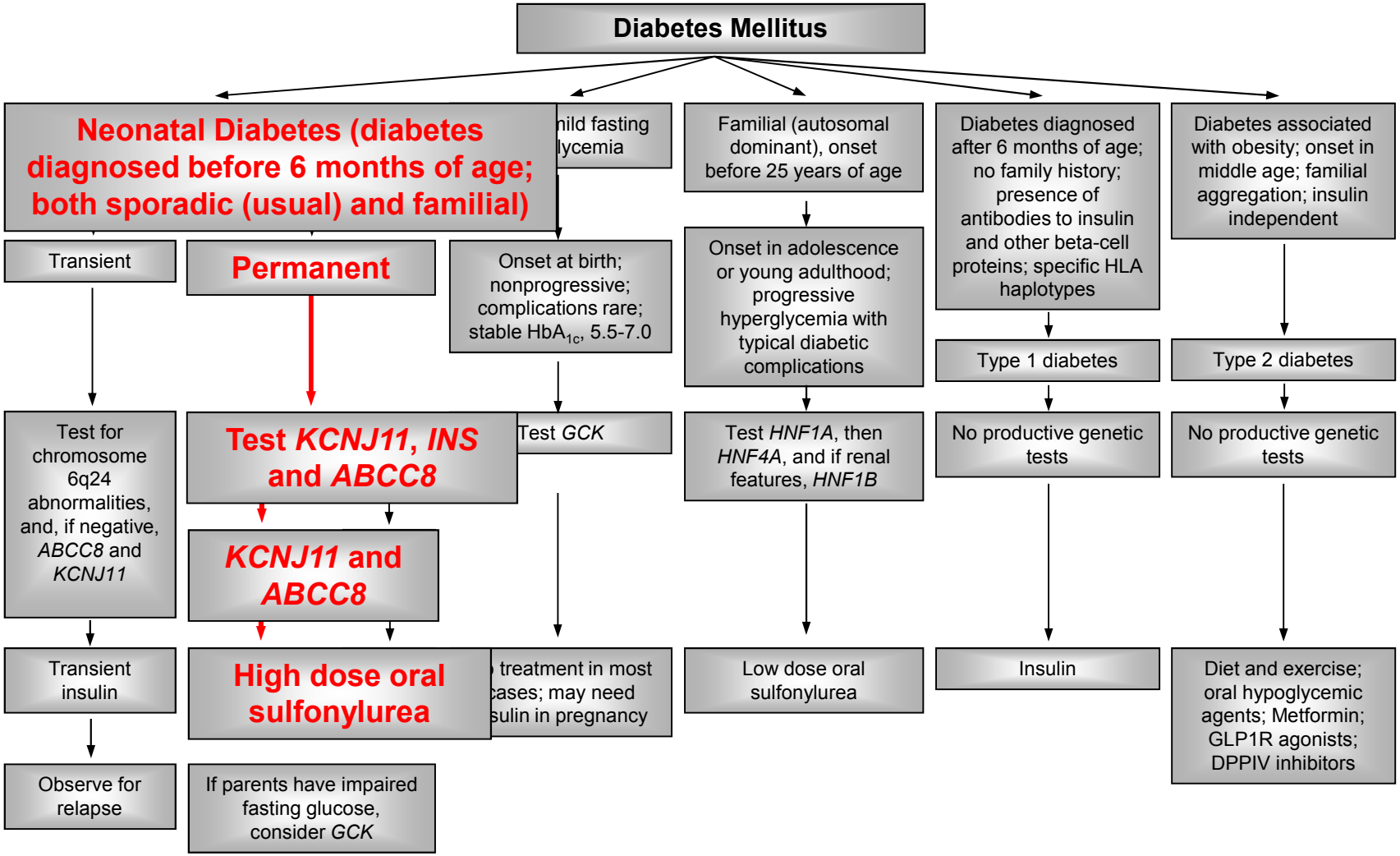
Genetic Studies of T2D: What's Next?

- T2D-GENES Consortium
- High throughput sequencing to discover low frequency and rare variants
- Project 1: Whole exome sequencing of 10,000 cases and controls from five major ethnic groups (African American, Mexican American, South Asian, East Asian and Northern European)
- Project 2: Deep (60x) whole genome sequencing on 568 members from 20 large Mexican American families (San Antonio Heart Study) extensively characterized for cardiometabolic phenotypes to exploit the value of pedigree information for the detection and interpretation of rare risk alleles.
- Results should establish the genetic architecture of T2D

Monogenic Diabetes and Personalized Genetic Medicine

- Frequently misdiagnosed as type 1 or type 2 diabetes
- Genetic testing is available and is beginning to be routinely used in some institutions when the patient is suspected to have a monogenic form of diabetes - personalized genetic medicine
- Correct diagnosis has a major impact on treatment

Application of Genetics for Clinical Decision Making and Patient Care



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'Miracle' unfolds for diabetic girl

Genetic discovery allows 6-year-old to swap insulin pump for readily available pill

By Peter Gorner
Tribune science reporter

When Lilly Jaffe, 6, gleefully disconnected her insulin pump from her hip last month, her mother, Laurie, forced herself to be brave.

Lilly was cutting the lifeline to the hormone that had kept her alive since she was a month old. That was when she was diagnosed with Type 1 diabetes, meaning she would always need insulin injections.

But thanks to advances in molecular medicine, doctors had reason to believe that Lilly could be weaned off the shots.

Tribune photo by Candice C. Cusic

Wyler Children's Hospital technician Karen Breedlove hugs former patient Lilly Jaffe, 6, whose diabetes was treated there.

Because scientists recently had identified the genetic mutation that causes her condition, they knew why her body was not making insulin and they had a way to fix it: a readily available drug.

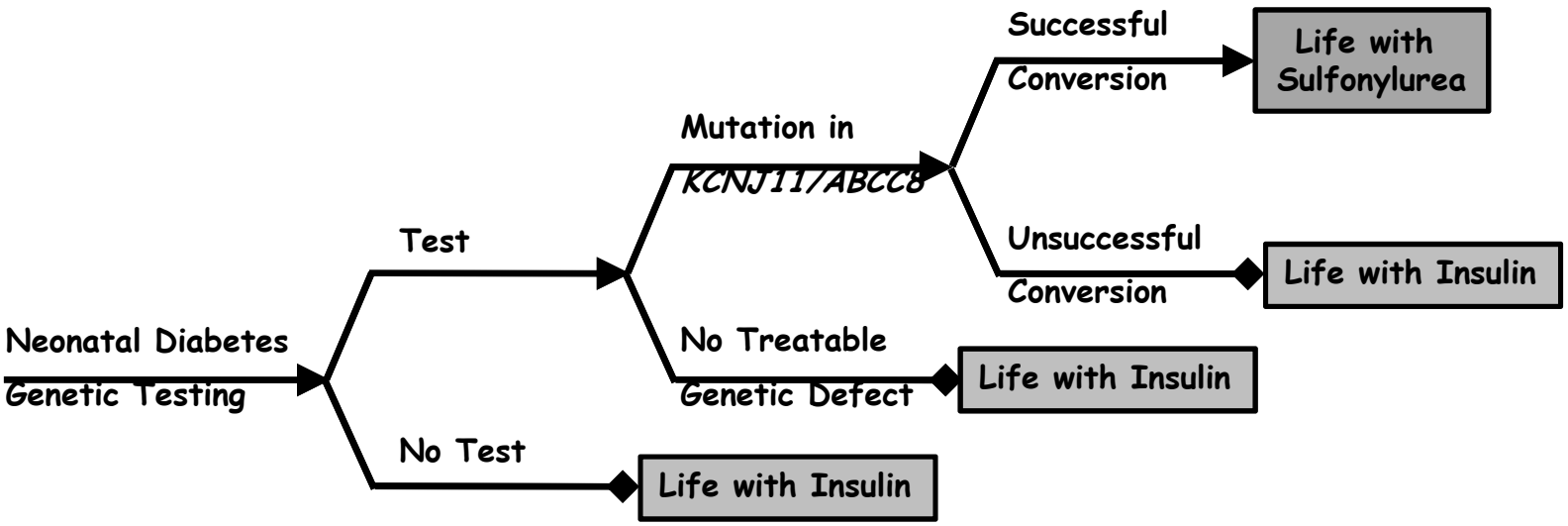
Now Lilly no longer needs in-

PLEASE SEE GENES, PAGE 13

Genetic Testing in Permanent Neonatal Diabetes

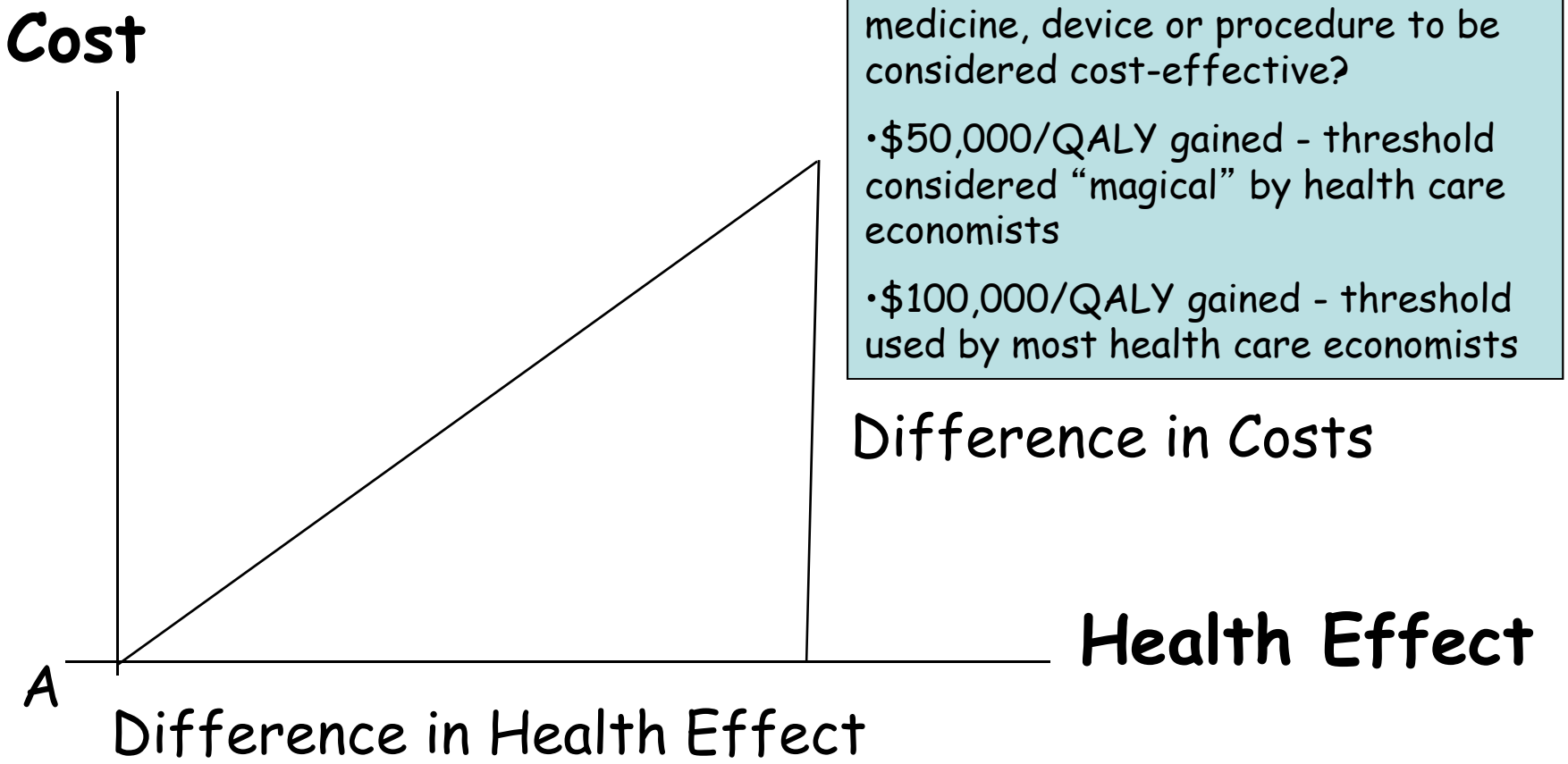
- Permanent neonatal diabetes is a rare form of diabetes (~1/150,000 - 250,000 live births).
- Mutations in the genes for the ATP-sensitive potassium channel (*KCNJ11* and *ABCC8*) which account for the largest fraction of cases allow patients to be switched from insulin to sulfonylurea therapy.
- Genetic diagnosis has major implications for treatment, overall control and quality of life.
- Is routine genetic testing for mutations a cost-effective policy and should it be supported by health care providers?

Decision Model for Economic Analysis for Genetic Testing in PNDM



	Time (yrs)	Testing	No Testing	Differences ($)
Quality-Adjusted Life Years, mean	10	7.64	7.32	0.32
	20	13.18	12.63	0.55
	30	16.99	16.29	0.70
Total Costs, mean, $	10	59,256	71,784	-12,528
	20	91,601	114,828	-23,227
	30	113,233	143,670	-30,437
Screening and Treatment Costs, mean, $	10	28,708	30,891	-2,183
	20	49,201	57,220	-8,019
	30	63,483	75,546	-12,063
Complication Costs, mean, $	10	9,484	14,978	-5,494
	20	17,854	27,411	-9,557
	30	25,211	37,937	-12,726
Indirect Costs, mean, $	10	21,065	25,916	-4,851
	20	24,550	30,204	-5,654
	30	24,550	30,204	-5,654
Incremental Cost-Effectiveness Ratio ($/QALY)	10	-39,394		--
	20	-42,876		--
	30	-43,335		--

Incremental Cost-Effectiveness Ratio (ICER) is a Slope



What is the ICER threshold for a new medicine, device or procedure to be considered cost-effective?

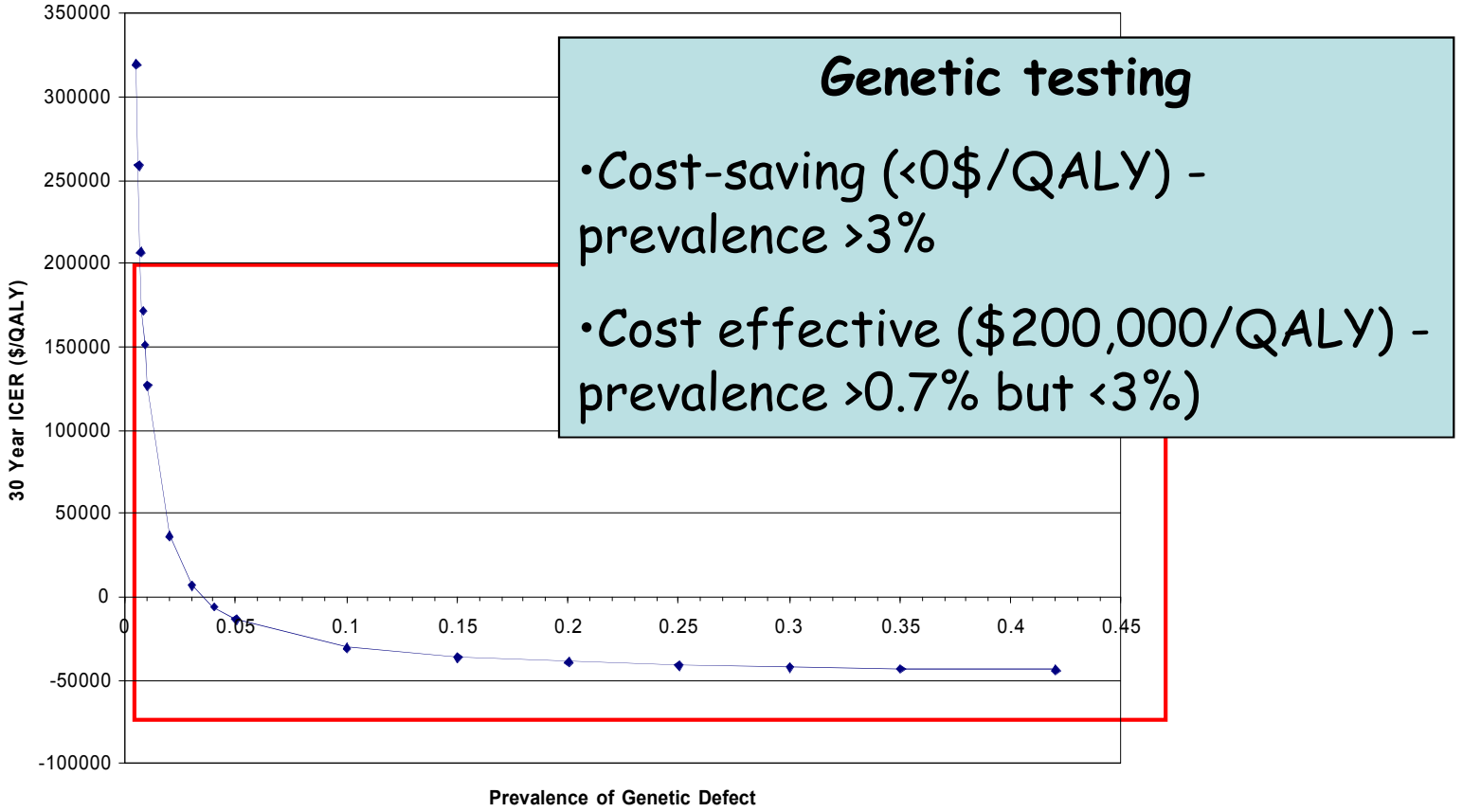
- $50,000/QALY gained - threshold considered "magical" by health care economists
- $100,000/QALY gained - threshold used by most health care economists

Incremental Cost-Effectiveness Ratio of Components of Diabetes Care

Intensive glucose control	$41,384/QALY
Intensive blood pressure control	-$1,959/QALY
Statin	$51,889/QALY

CDC Cost-Effectiveness Group. JAMA. 2002

Incremental Cost-Effectiveness Ratio by Prevalence of Treatable Genetic Defects



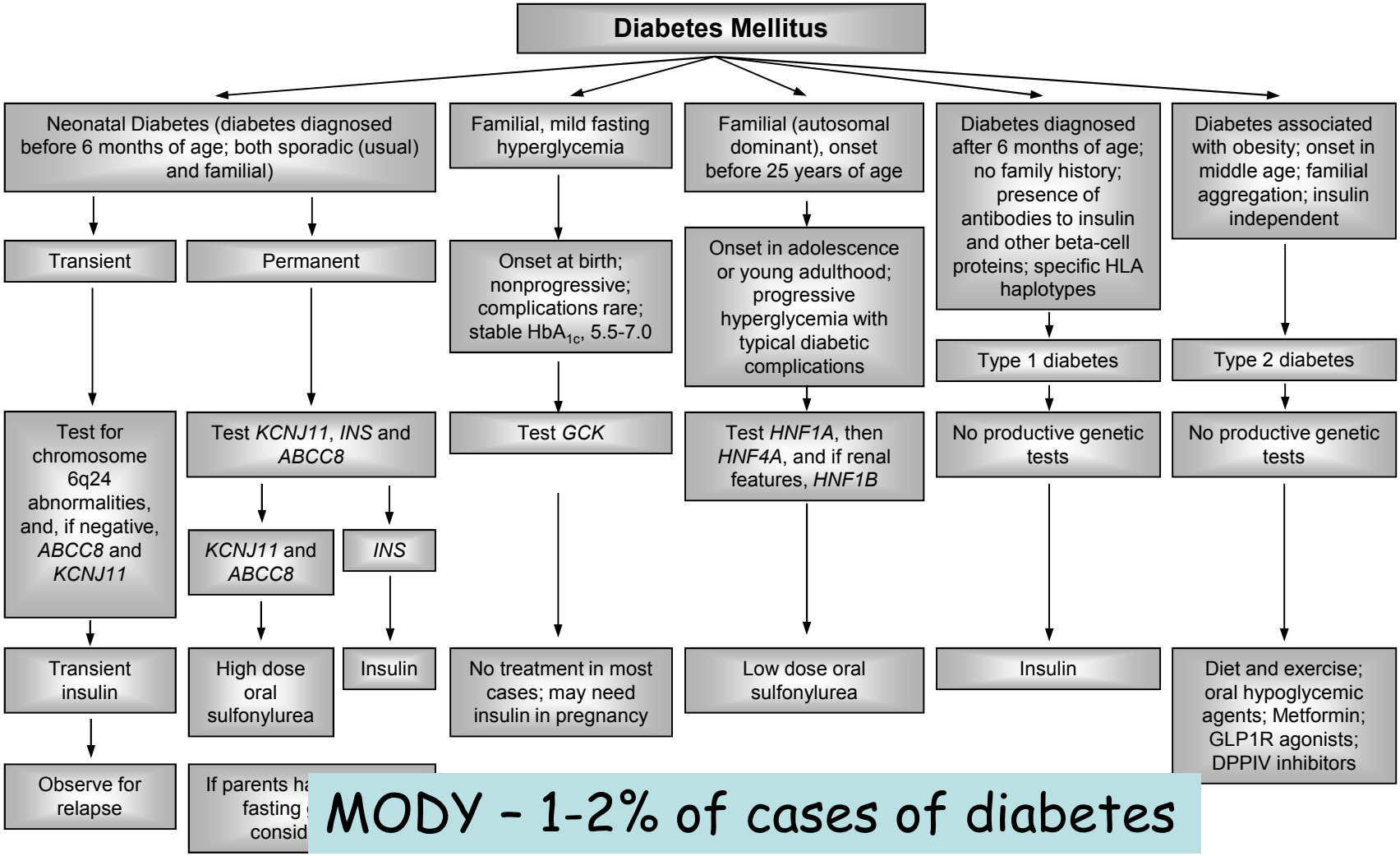
Genetic testing

- Cost-saving (<0$/QALY) - prevalence >3%
- Cost effective ($200,000/QALY) - prevalence >0.7% but <3%)

Routine Genetic Testing in Permanent Neonatal Diabetes

- Routine genetic testing for mutations in *KCNJ11* and *ABCC8* is cost-savings.
- Routine genetic testing should be the standard of care.

Application of Genetics for Clinical Decision Making and Patient Care



MODY – 1-2% of cases of diabetes

MODY

- Correct diagnosis has a major impact on treatment, prognosis and genetic counseling
- Most common causes are mutations in the heterogygous state in HNF1A, GCK, HNF4A and HNF1B (and ABCC8)
- Genetic diagnosis is important for genetic counseling for all forms of MODY
- Genetic diagnosis is important for treatment of HNF1A (SU), GCK (none required), HNF4A (SU) and ABCC8 MODY (SU)

Barriers to Diagnosing MODY

- Identifying patients who may have MODY
  - Clinical overlap with type 1 and type 2 diabetes
- Obtaining genetic testing
  - Limited understanding of clinical implications
    - Physicians
    - Patients
    - Insurance companies
  - Costs and limited insurance coverage for genetic testing
  - Certified genetic testing (research testing vs clinical testing; government certification)

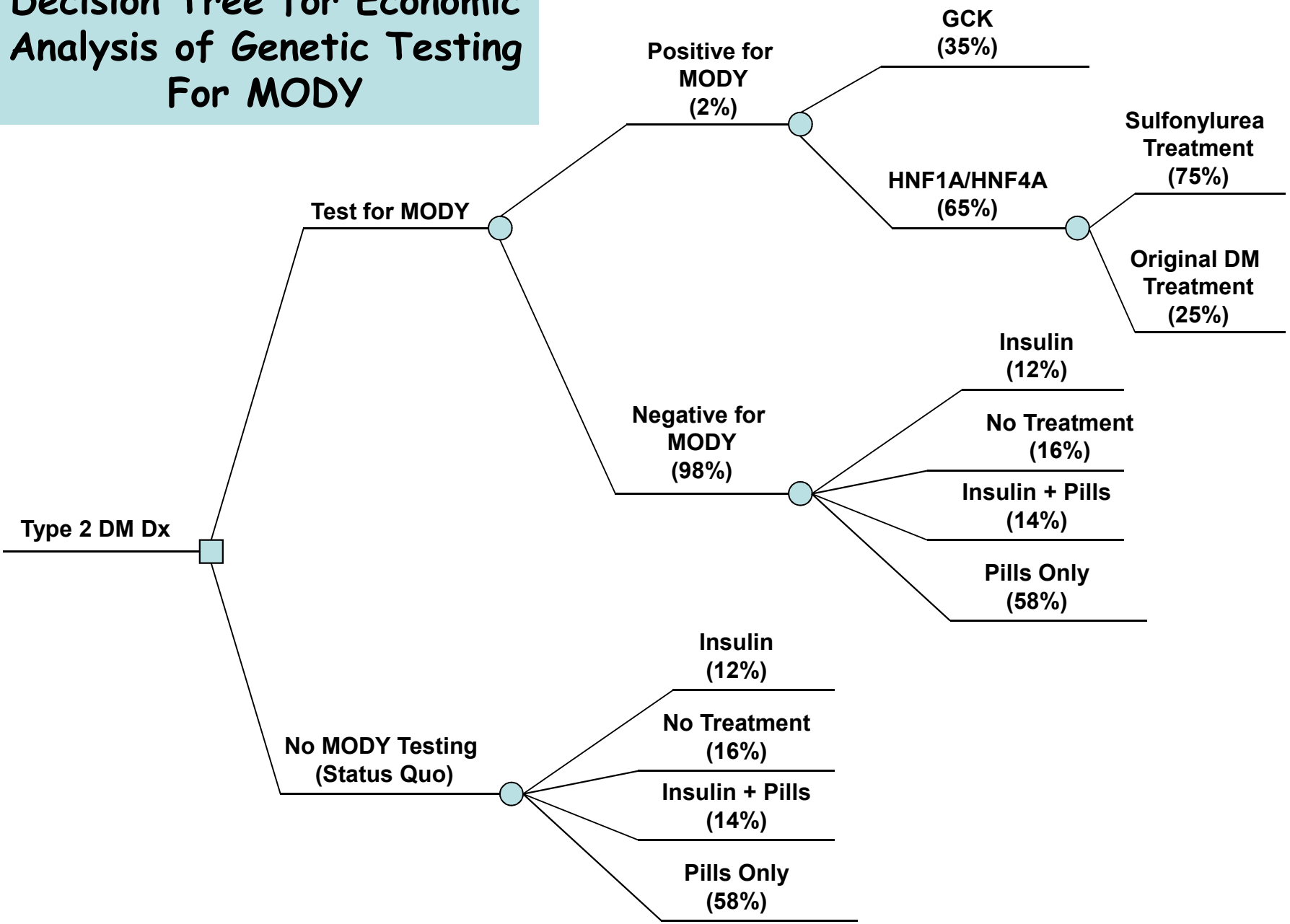
Opportunities for Diagnosing MODY

- Identify patients who may have MODY
  - Genetic diagnosis affects treatment
- Improve understanding of implications of genetic testing
  - Physicians
  - Patients
  - Insurance companies
- Implement genetic testing as standard of care

Genetic Testing and MODY

- Increased awareness of MODY by endocrinologists is beginning to used used when the patient is suspected to have MODY
- MODY calculator (www.diabetesgenes.org) can be used to predict likelihood of MODY
- Routine genetic testing for MODY in **ALL** patients with a diagnosis of diabetes?

Decision Tree for Economic Analysis of Genetic Testing For MODY



Genetic Testing and MODY

- In the context of health care costs in the United States (data upon which model is built), routine genetic screening for GCK-, HNF1A- and HNF4A-MODY in incident cases of type 2 diabetes is a cost-effective use of personalized genetic medicine if we can
  - Preselect patients for testing; i.e. increase the prevalence from 2% of cases to 30% of cases; and/or
  - Reduce the cost of the test ($2,000+ to $600)

What's Next?

- Improve pick-up rate
  - Clinicial education
  - a "MODY calculator"
- Improve "quality" of reports to the physician

Lessons

- Diabetes can be a primary genetic disorder.
- Genetics can provide a better understanding of the genes and pathways involved in the development of diabetes.
- Genetics can improve diagnosis and treatment for monogenic forms of diabetes.
- Diabetes is a model for personalized genetic medicine.
- Studies of monogenic forms of diabetes are more fun!