Welcome

Martha Brumfield, President & CEO

T1D
CRITICAL PATH INSTITUTE

November 7, 2016

CRITICAL PATH
INSTITUTE

Objectives

- Introduce goals of qualifying with regulatory authorities islet autoimmune markers in T1D
- Provide information on C-Path and how the consortium model works
- Provide information about the qualification process
- Achieve consensus on a path forward and garner interest in participating in this effort

Agenda

Time	Topic	Presenter(s)
11:30 AM	Registration and Lunch	
12:00 PM	Welcome and Introductions • Meeting objectives Initial Project Proposal	Martha Brumfield, C-Path Jessica Dunne, JDRF
12:45 PM	C-Path Overview • Q & A	Martha Brumfield, C-Path
1:15 PM	FDA Perspective on Biomarker Qualification • Q & A	Dr. Shashi Amur, FDA
2:30 PM	BREAK	
2:45 PM	Consortium Formation/ Structure • Q & A	Steve Broadbent, C-Path
3:15 PM	Investigator Perspective • Q & A	Dr. Åke Lernmark, Lund University
4:00 PM	Open Discussion	
4:45 PM	Summary and Next Steps • Call to Action	Steve Broadbent, C-Path
5:00 PM	Adjourn	Martha Brumfield, C-Path

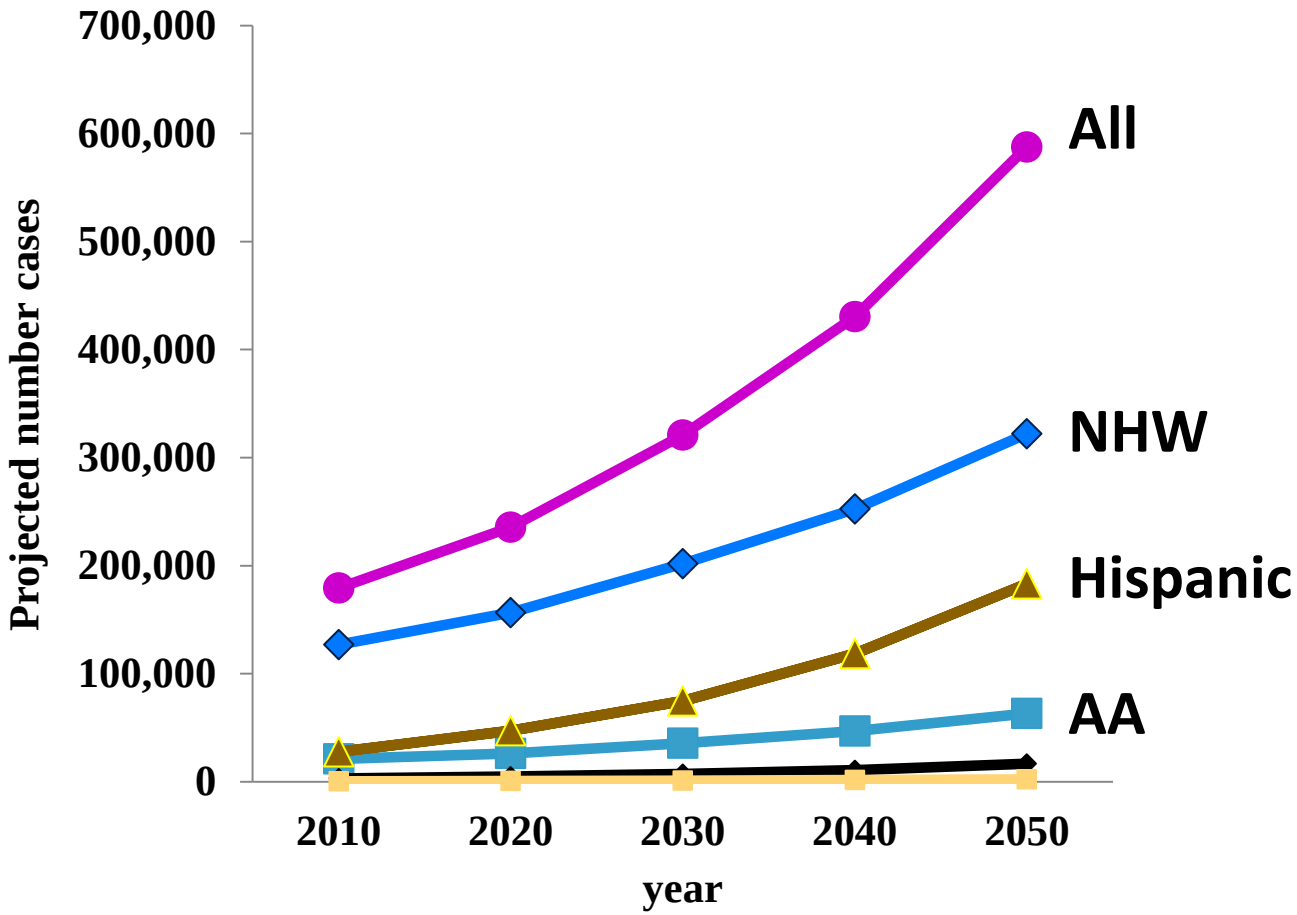
Qualification of Autoantibodies for T1D

Jessica Dunne, Ph.D.

JDRF

November 7, 2016

Projected Number of Youth < 20 Years With T1D: Increased Incidence Scenario

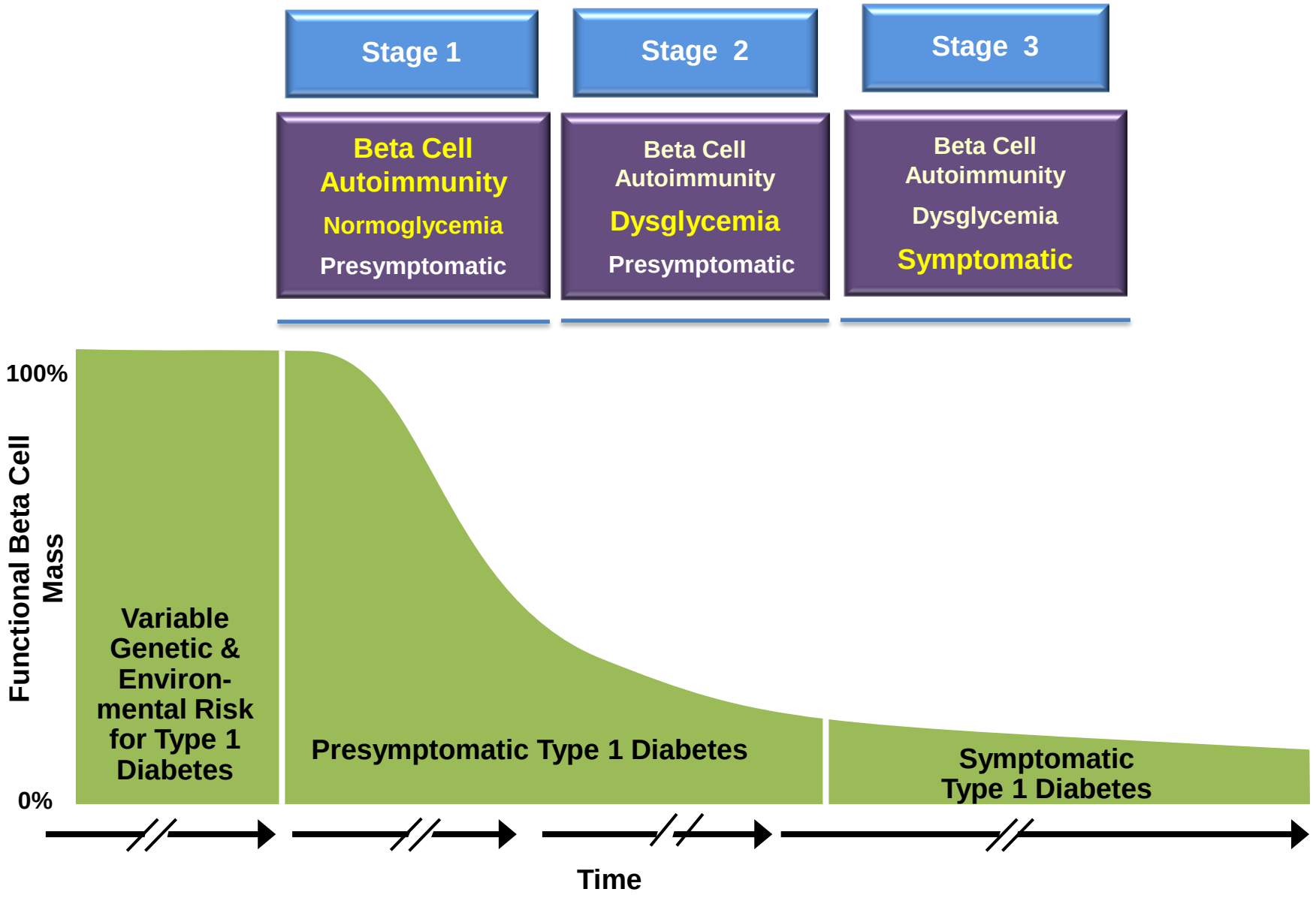


- Number of US youth with T1D projected to increase 3.3-fold by 2050
- Highest among NHW youth (7.04/1000 in 2050)
- Largest relative increase among Hispanic youth (6.6-fold increase)
- US health care systems need to be prepared

Imperatore, et al. *Diabetes Care,* 35(12), 2515, 2012

Scientific Framework of Staging of T1D

- T1D is a disease continuum that begins prior to symptomatic disease
- Risk of developing T1D can be identified and quantified
- T1D has well-defined, reproducible early stages that reach a point of inevitability for symptomatic T1D
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy
- The ability to screen for risk and stage T1D prior to symptomatic T1D provides a unique opportunity to delay, and ultimately prevent, symptomatic T1D



Diabetes Care. 2015 Oct;38(10):1964-74

Why Change the T1D Diagnostic Criteria?

- Current benefits of risk detection
  - Decreased risk of DKA and hospitalization at diagnosis
  - Greater levels of residual functional beta cell mass at time of initiation of insulin replacement may lead to long-term benefit
- Provides a framework to inform benefit/risk evaluation for regulatory, reimbursement, and clinical care
- Improve the design of prevention trials
- Catalyze risk screening and increase enrollment in natural history and prevention clinical trials

Early Stages of Type 1 Diabetes

Stage 1: Beta Cell Autoimmunity+/Dysglycemia–/ Presymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Beta Cell Autoimmunity+/ Dysglycemia+/ Presymptomatic T1D

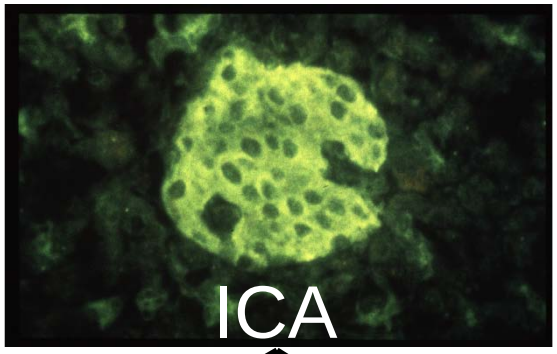
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Islet Autoantibodies in T1D

1st generation assays

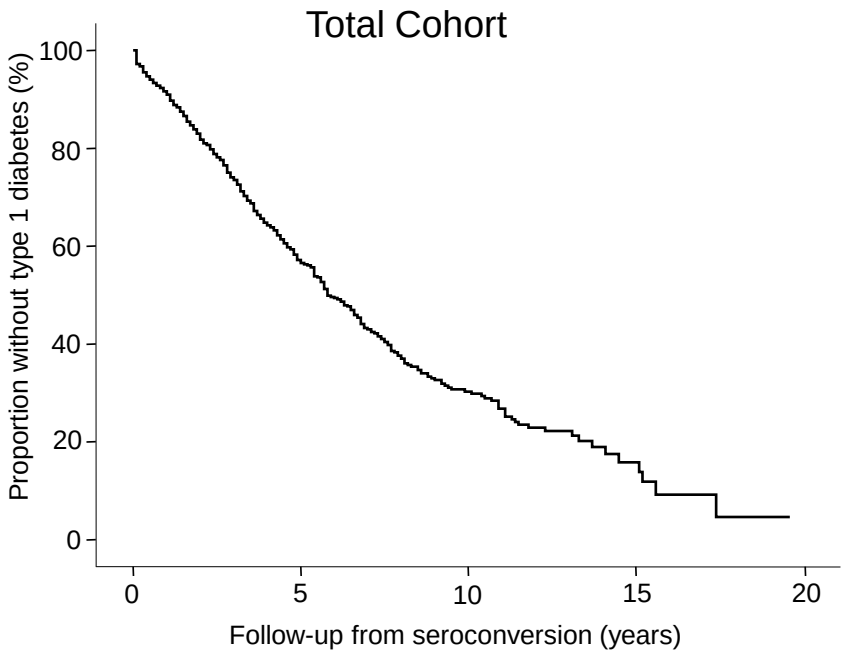


Insulin autoantibodies

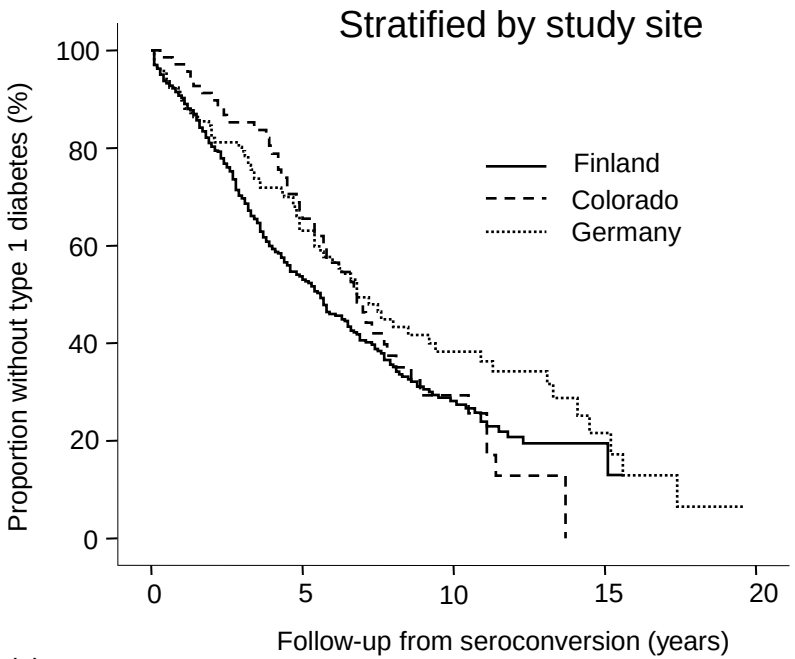
2nd generation (RIA, ELISA)

ZnT8A | **IA-2A** | **GADA** | **mIAA**

Progression to Symptomatic Stage 3 Type 1 Diabetes from Time of Islet Autoantibody Seroconversion in Stage 1 At-Risk Children with Multiple Islet Autoantibodies



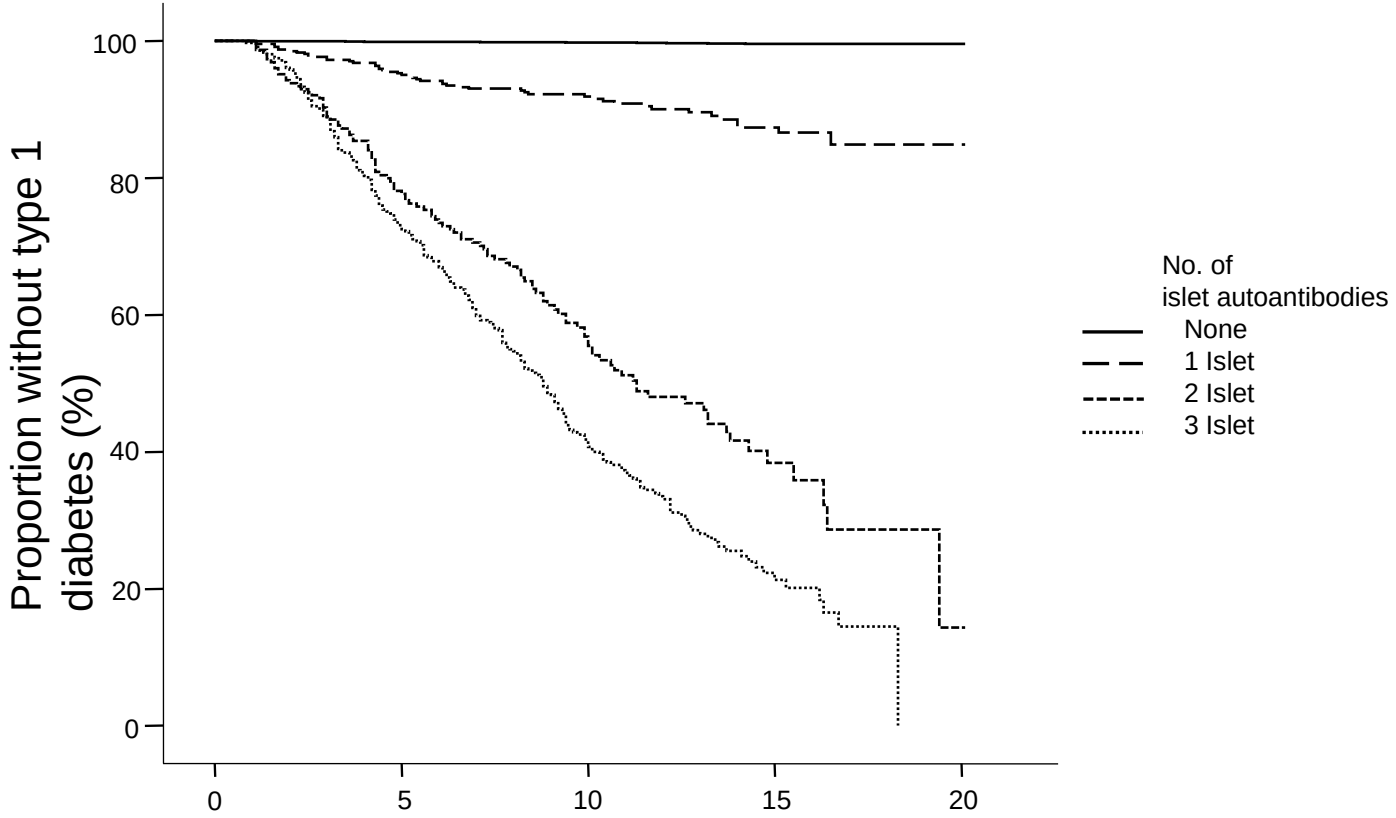
No. of events				
No. at risk	585	257	70	8
Diabetes		236	95	20
Lost to follow-up		92	92	42



No. at risk				
Colorado	69	38	8	0
Finland	399	158	41	3
Germany	117	61	21	5

JAMA. 2013;309(23):2473-2479

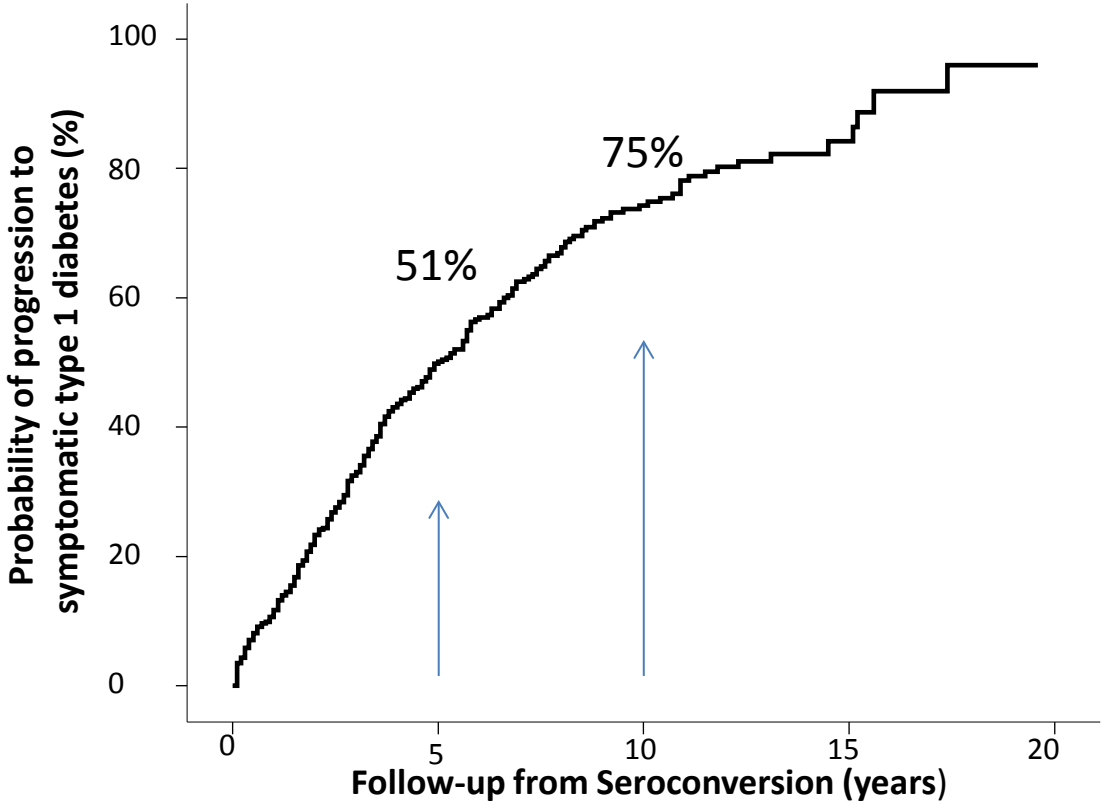
Probability of Progression to Stage 3 Symptomatic T1D Stratified for Number of Islet Autoantibodies from Birth



No. of events					
Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

JAMA. 2013;309(23):2473-2479

5- and 10-Year Risk of Progression to Symptomatic T1D with Multiple Islet Autoantibodies ≤ Age 5 Years is 51% and 75%

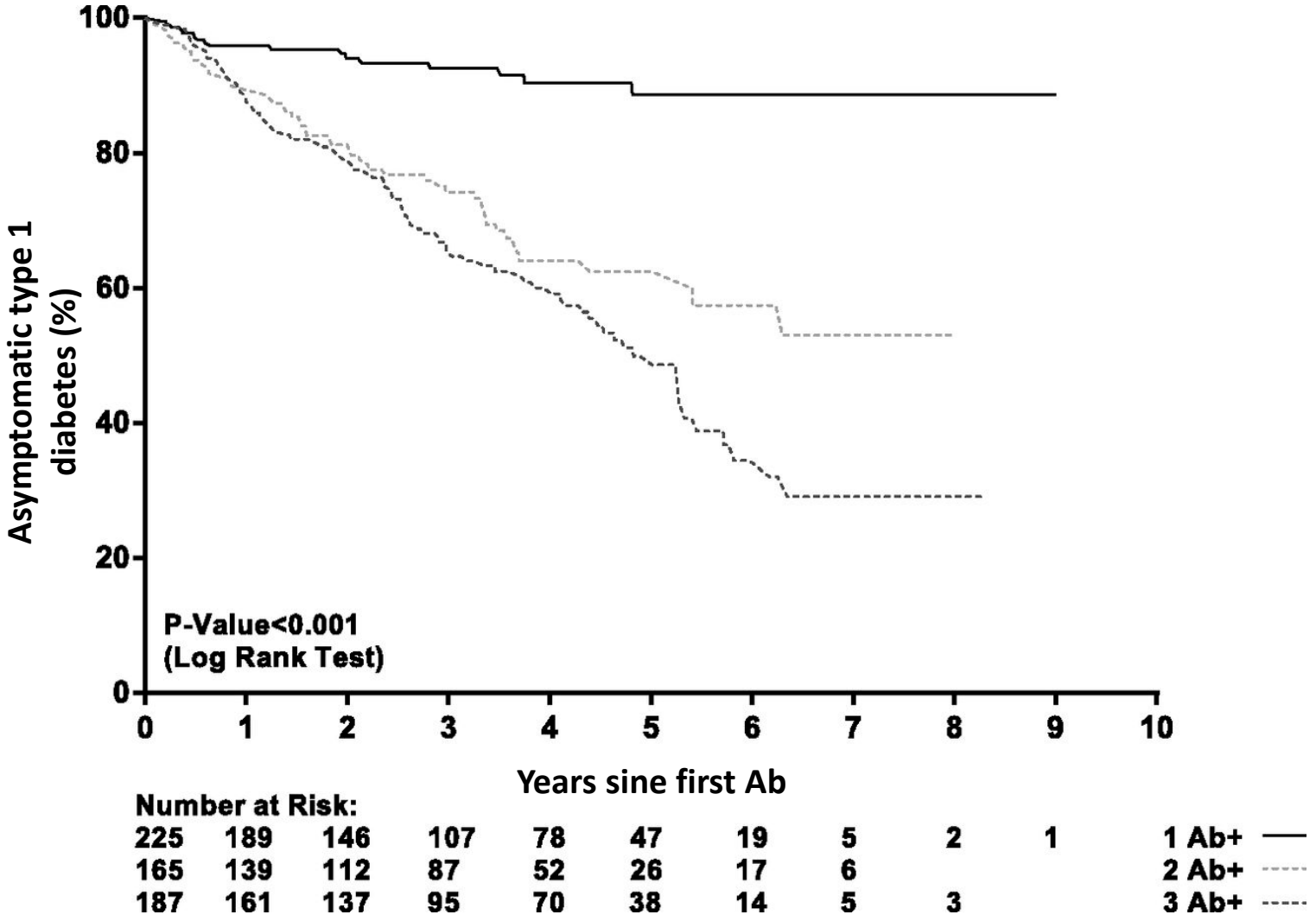


Lifetime Risk Approaches 100%

George Eisenbarth ***"The clock to T1D has started when islet antibodies are first detected".*** **Paradigm shift for staging of type 1 diabetes before clinical onset**

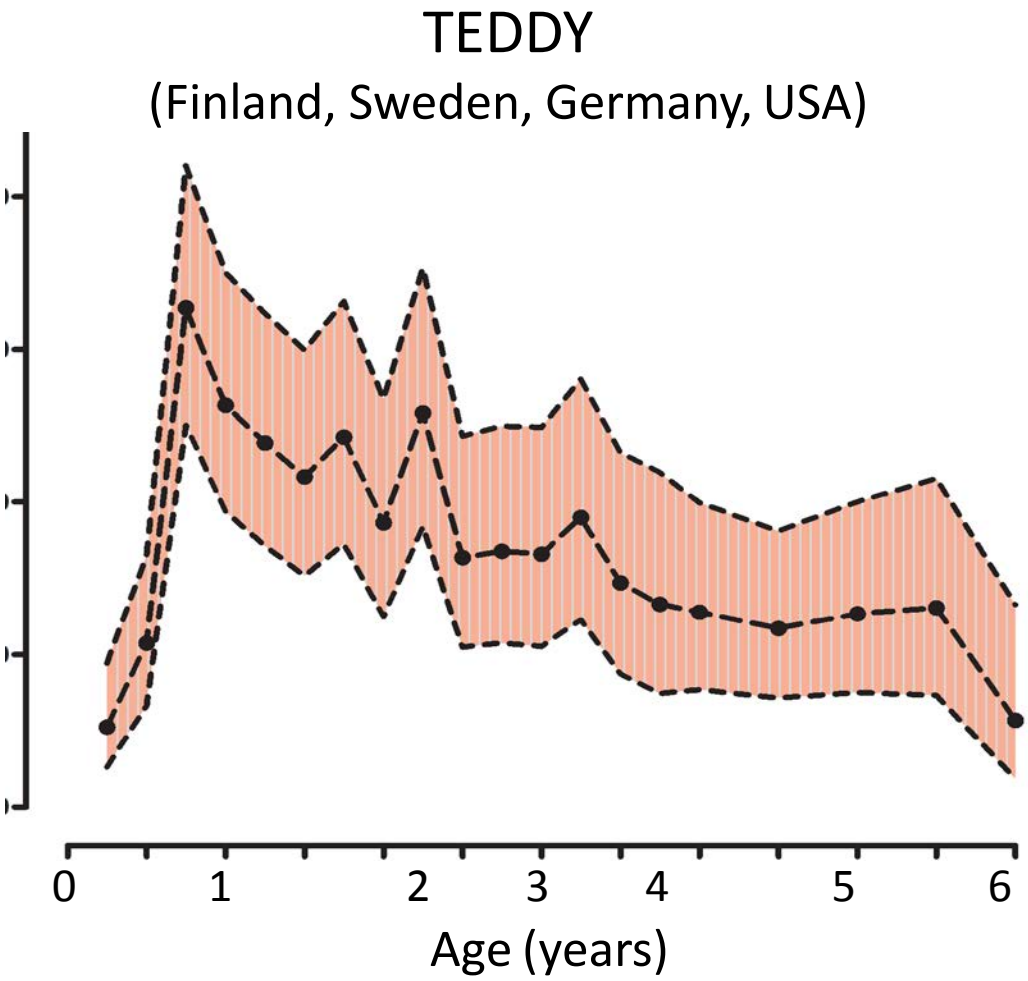
JAMA. 2013;309(23):2473-2479

Progression to Diabetes in Children with Confirmed Autoantibodies



Andrea K. Steck *et al. Dia Care* 2015;38:808-813

Early Islet Autoantibody Seroconversion Incidence Peak



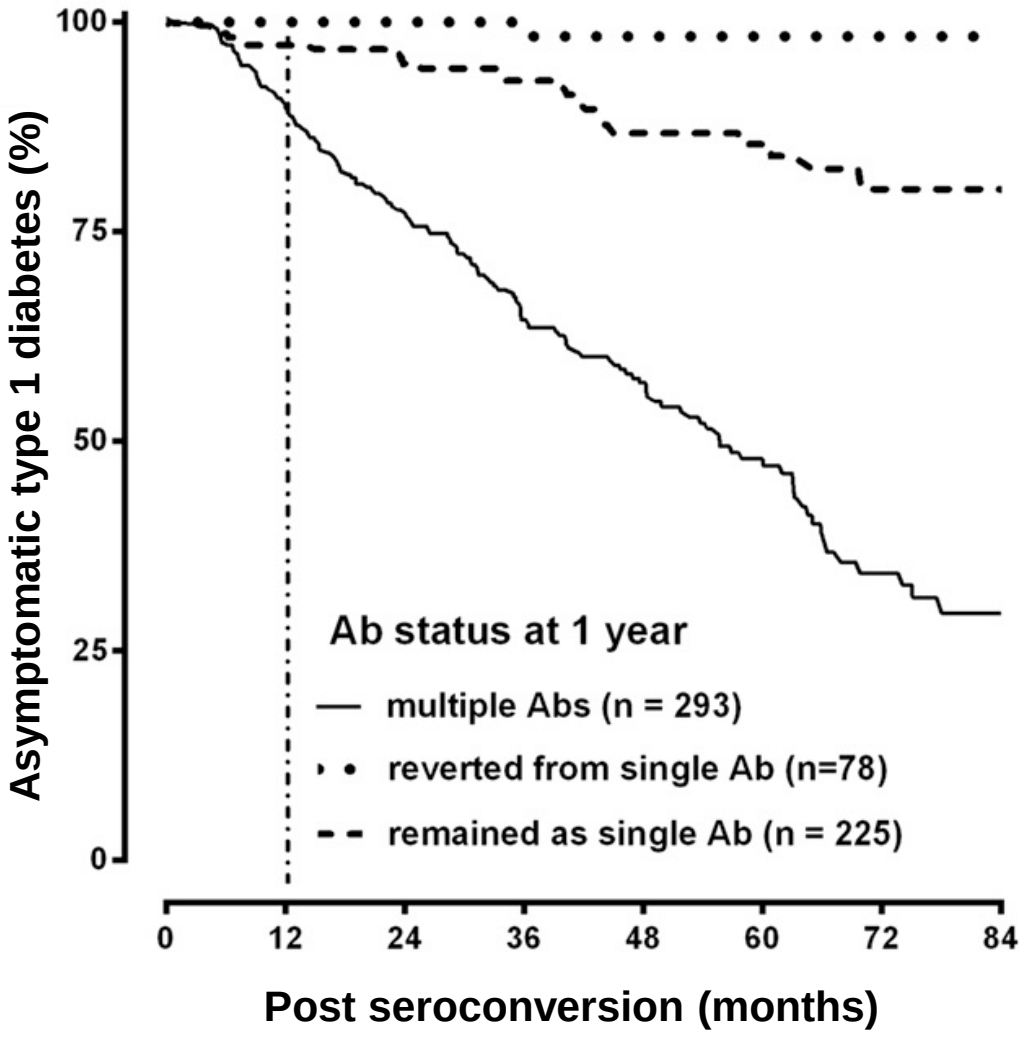
TEDDY *study,* 2015

What About AAb Reversion?

Max number of persistent AAbs during follow-up	Total N	AAb reversion pattern during follow-up	N (% of total)	Developed T1D (N)
Single (1 AAb)	225	Reverted	99 (44%)	1
Multiple (2 AAbs)	161	Reverted 2 AAbs	4 (2.5%)	2
Multiple (3 AAbs)	210	Reverted 3 AAbs	1 (0.5%)	1

Vehik et al., *Diabetes Care* 2016;39:9:1535-42

AAb Reversion and Disease Progression



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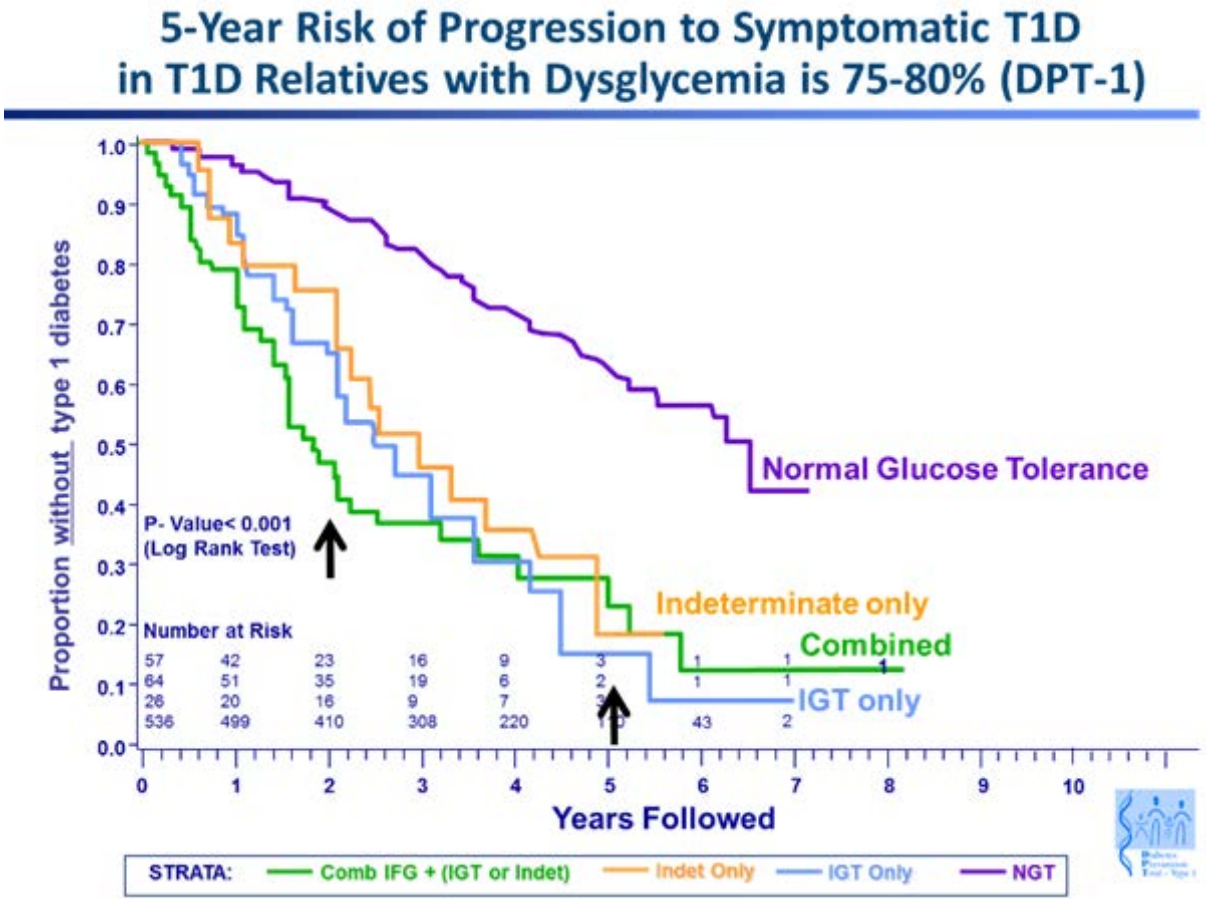
Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

	5-Year Risk	Prevalence
Abnormal Oral Glucose Tolerance Test	**75-80%**	**0.7%**



N Engl J Med 2002;346:1685–1691
Diabetes Care 2005;28:1068–1076

*Data includes both children and adults

Early Stages of Type 1 Diabetes: Diagnostic Criteria

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic	Stage #3 New Onset Symptomatic T1D
Diagnostic Criteria	▪ Multiple AutoAbs ▪ No impaired glucose tolerance or impaired fasting glucose	▪ Multiple AutoAbs ▪ Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose • FPG >100 mg/dL • OGTT: 2h PG ≥140mg/dL; 30, 60, 90 min PG ≥200 mg/dL • Random plasma glucose ≥200 mg/dL • HbA1c ≥5.7% • Increasing HbA1c	▪ Clinical Symptoms

- **Why is screening important?**
  - By getting screened, you may:
    - Enter a prevention trial
    - Avoid hospitalization
    - Help researchers to closely monitor disease progression.
- **Who is eligible?**
  - Anyone between the ages of 1 and 45 years with a sibling, child or parent with type 1 diabetes.
  - Anyone between the ages of 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with type 1 diabetes.
- **http://www.pathway2prevention.org/**

Stages of Type 1 Diabetes and the Use of AAbs in Clinical Trial Design

Pre-Stage 1: Individuals at-risk for T1D

General population – 0.4%

Individuals with high-risk genes – 4%

First-degree relatives – 3-8%

Interventions during pregnancy

Interventions at birth/universal interventions

Childhood interventions to highest-risk individuals

Stage 1: Beta Cell Autoimmunity/Normoglycemia/Presymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Abatacept Prevention Trial

Stage 2: Beta Cell Autoimmunity/Dysglycemia/Presymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Teplizumab Prevention Trial

Stage 3: Beta Cell Autoimmunity/Dysglycemia/Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

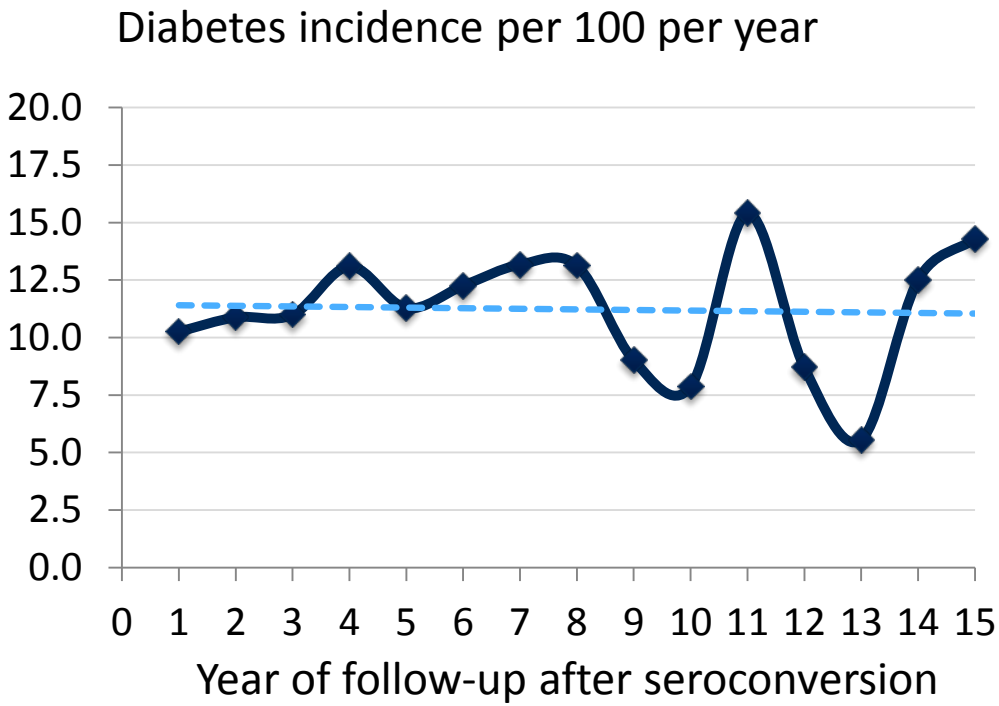
Potential Context of Use Statement for AAbs Regulatory Qualification

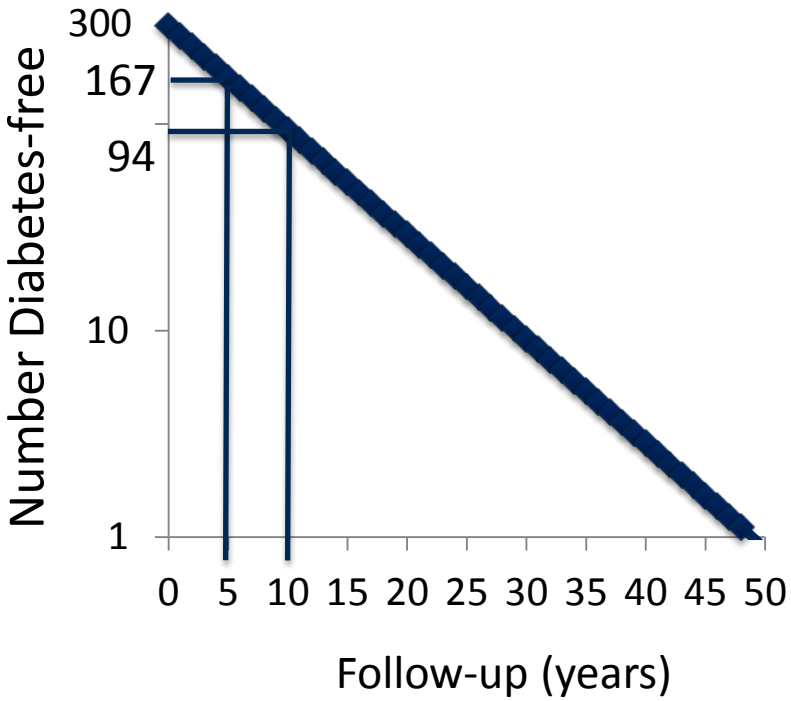
- Multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, or three variants (R, W or Q on position 325) of the ZnT8 transporter are a prognostic marker for disease progression in presymptomatic type 1 diabetes (T1D). The beta cell autoantibodies may be used as an enrichment factor for the design of clinical trials and identification of subjects likely to benefit from interventions being developed for delay of the clinical onset or prevention of symptomatic type 1 diabetes.

BACK-UP SLIDES

Estimated Progression to Symptomatic T1D

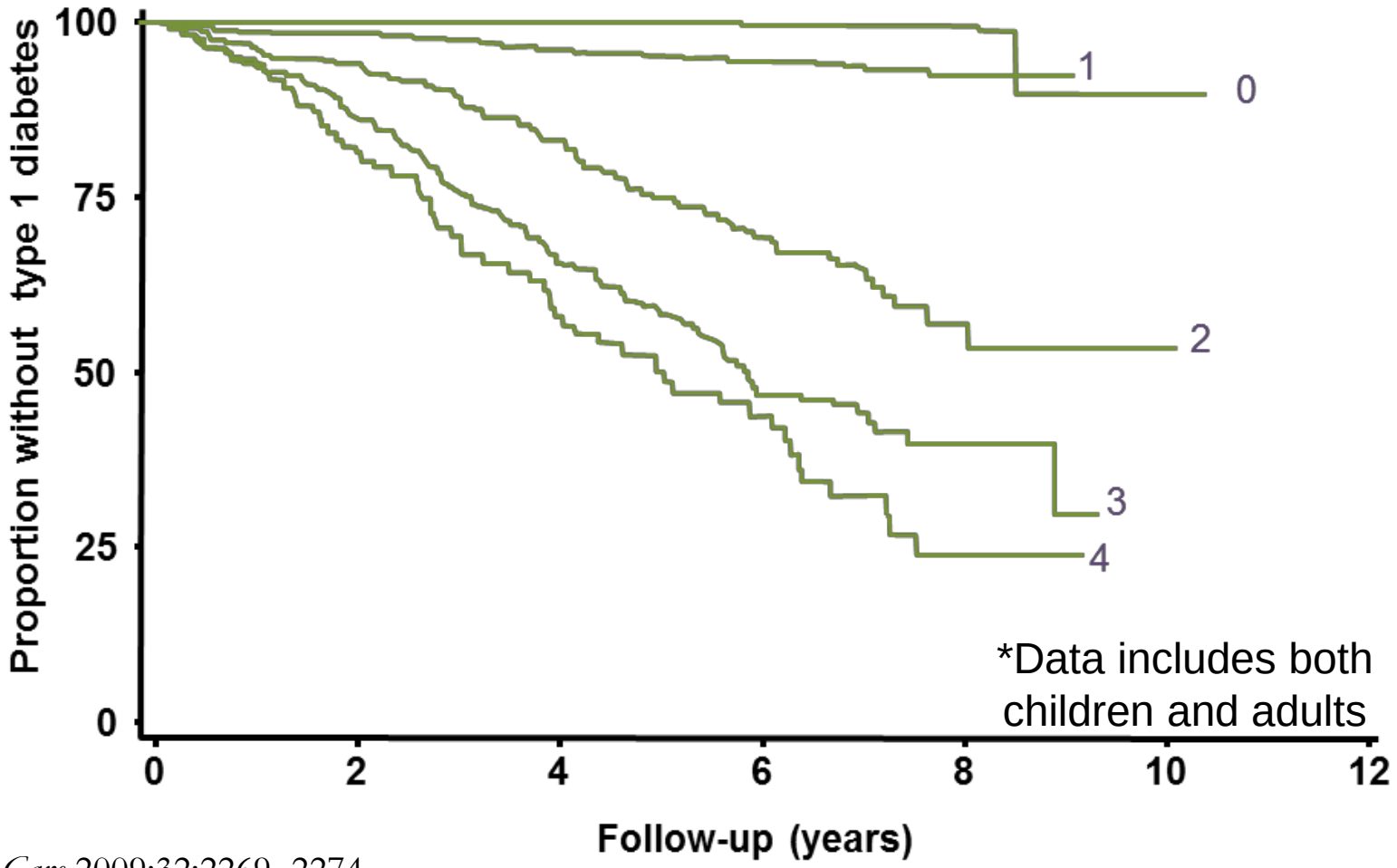
Risk is persistently around 11% per year





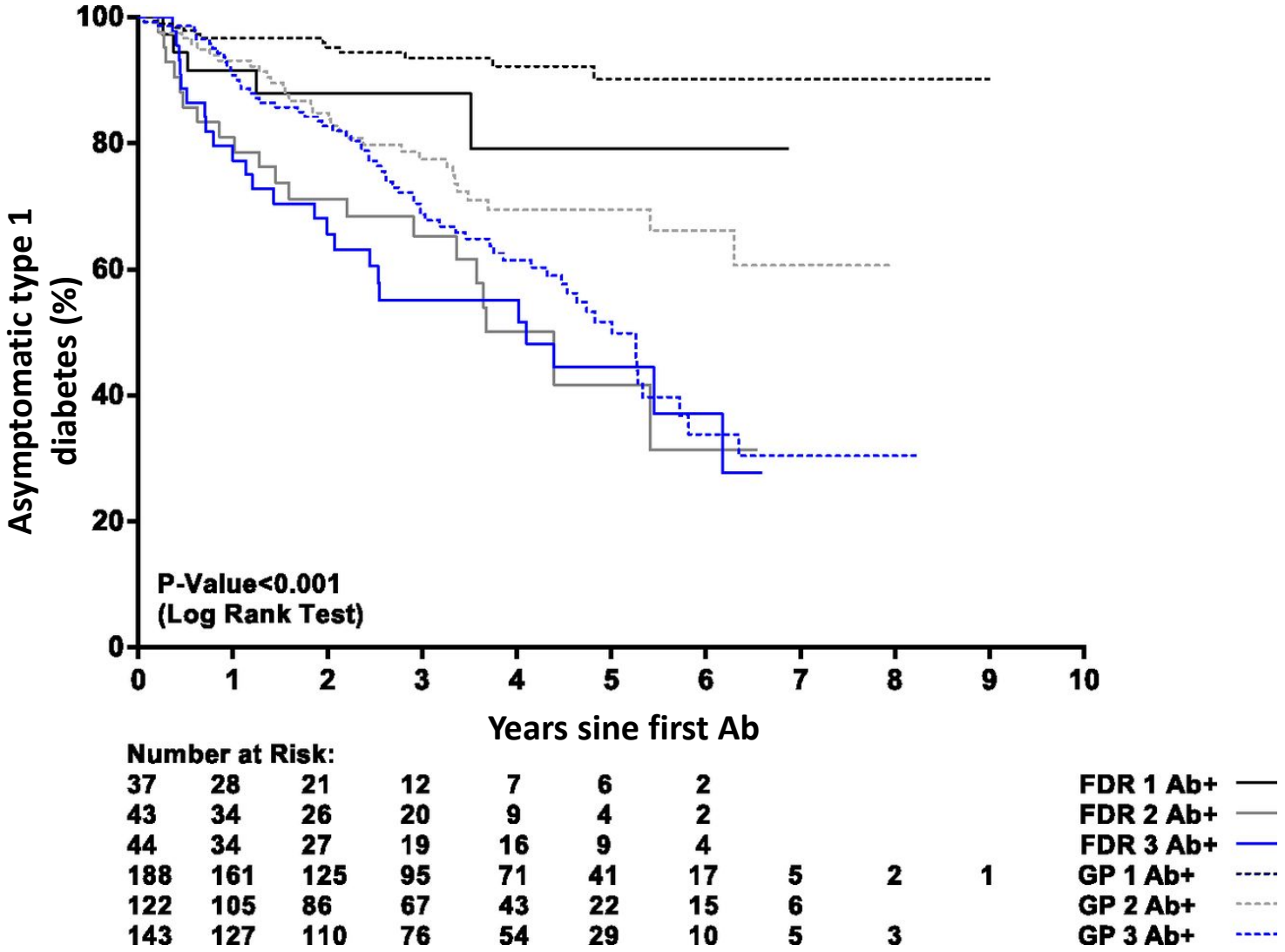
Bonifacio and Ziegler

Probability of Progression in Islet Autoantibody Positive Relatives of Individuals with T1D Stratified for Number of Autoantibodies (DPT-1)



Diabetes Care 2009;32:2269–2274

Progression to Diabetes in Children Expressing One, Two, or Three Autoantibodies by Family History.



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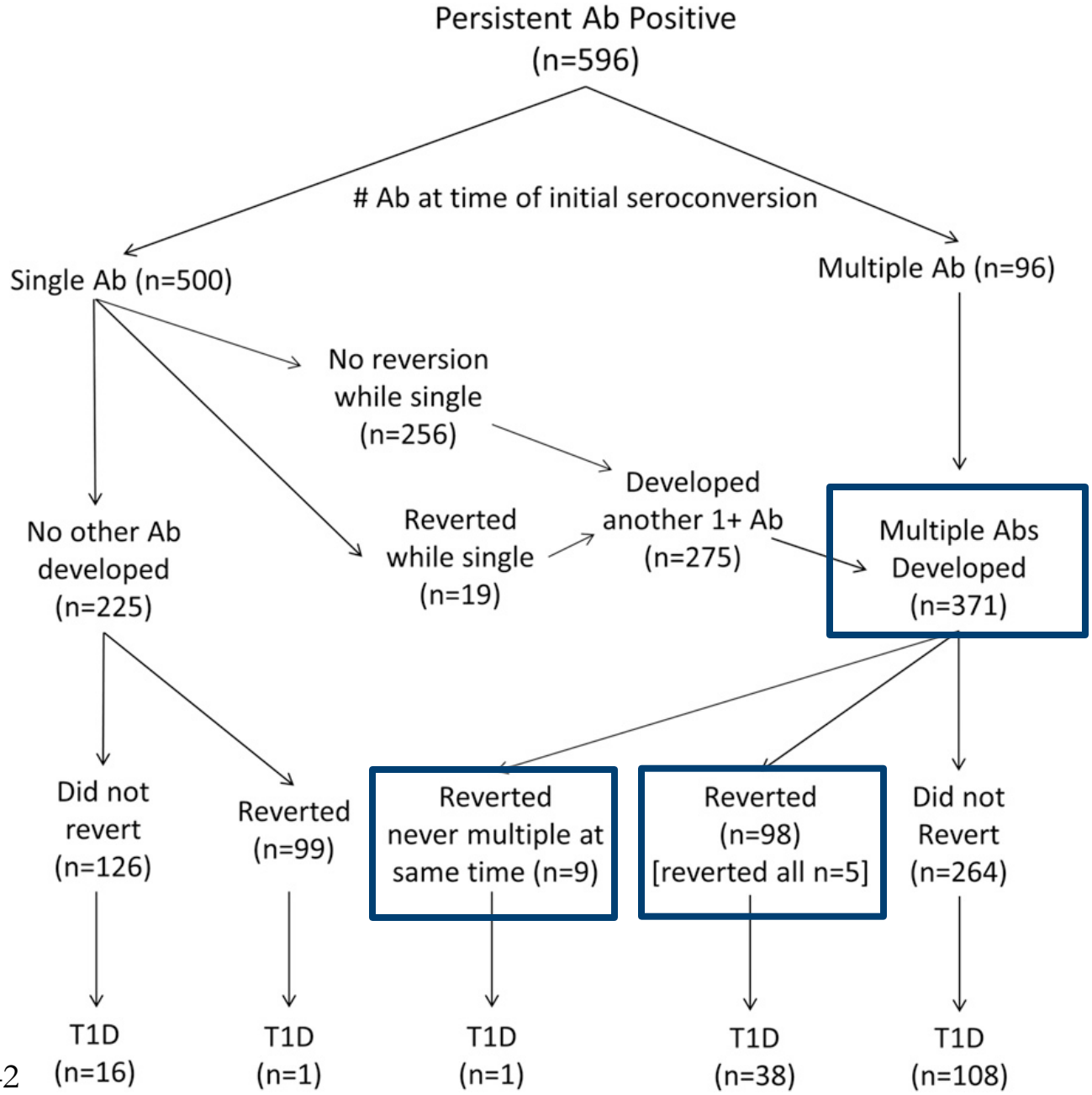
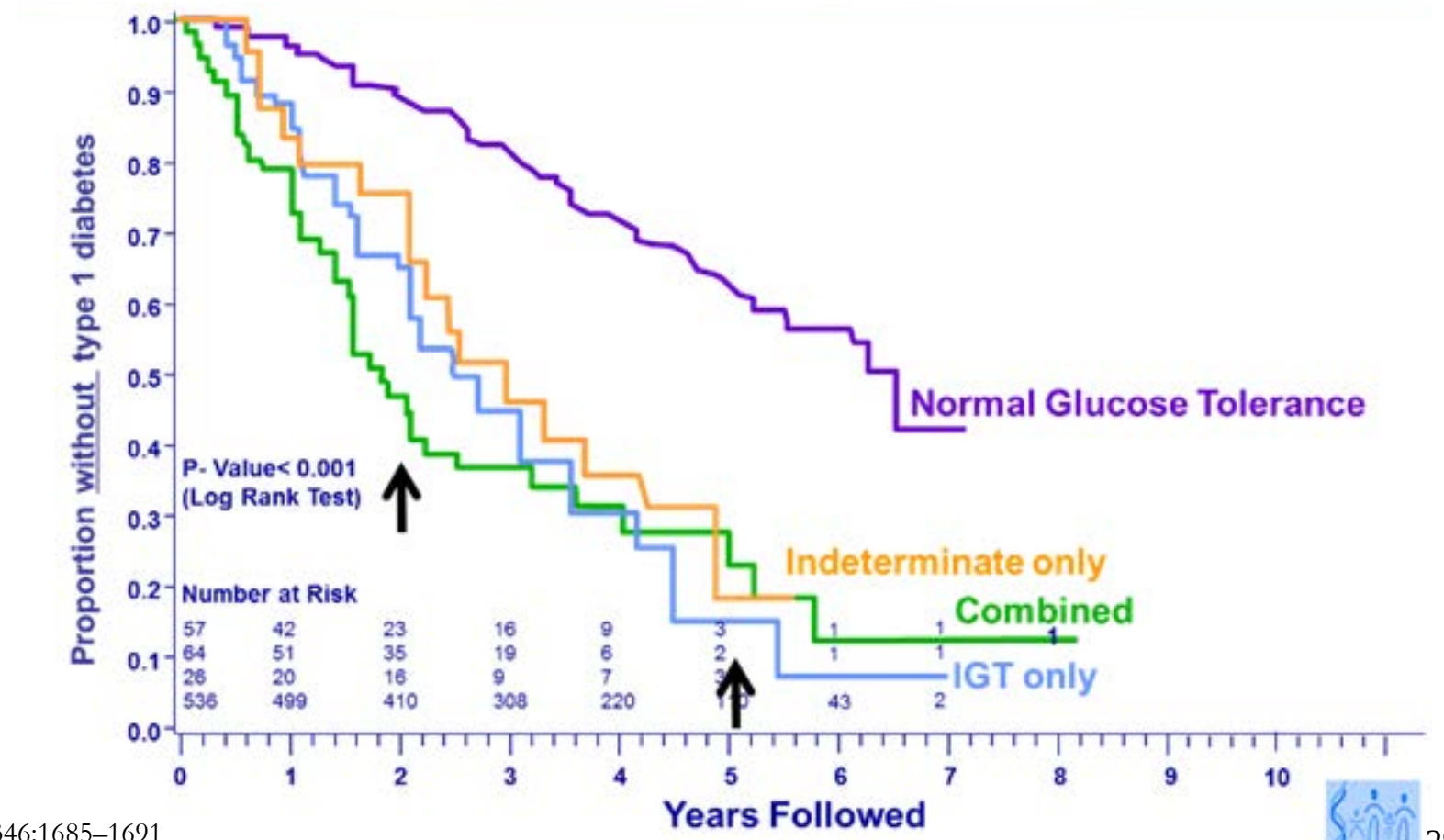


Vehik et al.,
Diabetes Care
2016;39:9:1535-42

5-Year Risk of Progression to Symptomatic T1D in T1D Relatives with Dysglycemia in 75-80% (DPT-1)

	5-Year Risk	Prevalence
Abnormal Oral Glucose Tolerance Test	**75-80%**	**0.7%**

*Data includes both children and adults



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Diabetes Care 2005;28:1068–1076

Early Stages of Type 1 Diabetes: Potential Clinical Trial Endpoints

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic
Potential Endpoints of Clinical Trials	▪ Dysglycemia prevented ▪ Autoimmunity regulated ▪ Symptoms delayed, Insulin dependence delayed, prevented	▪ Dysglycemia reversed ▪ FPG normalized ▪ IGT fails to progress to IFG ▪ HbA1c restored to normal levels; Increasing HbA1c reversed ▪ Autoimmunity regulated ▪ Symptoms delayed; Insulin dependence delayed, prevented

Beta Cell Autoantibody Qualification Consortium

Martha Brumfield, President & CEO

T1D CRITICAL PATH INSTITUTE

November 7, 2016

CRITICAL PATH INSTITUTE

Topics

- History of C-Path, What We Do and How We Do It
- What is Qualification?
- What this Consortium Can Do and What It Will Not Do
- C-Path Experience with Data Sharing and Aggregation
- C-Path Track Record

C-Path Mission

The Critical Path Institute is a catalyst in the development of tools to advance medical innovation and regulatory science, accelerating the path to a healthier world. We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science.

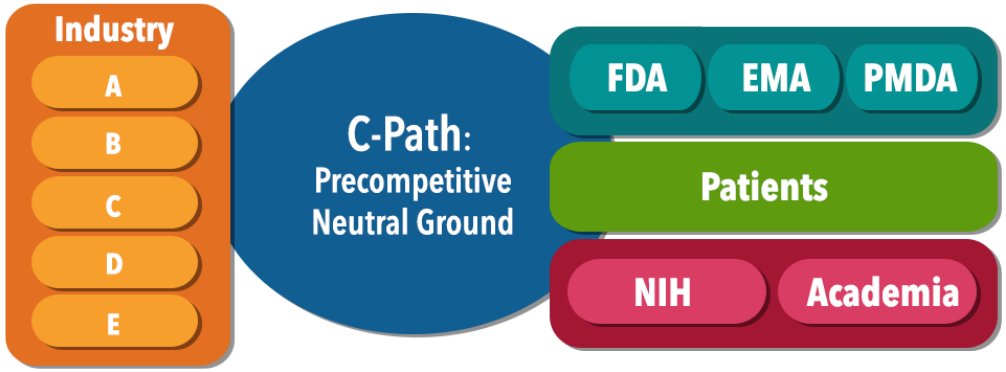
Critical Path Initiative

Independent 501(c)3 founded in 2005 "… to foster development of new evaluation tools to inform medical product development"

Memorandum of Understanding created between the FDA and C-Path in 2005

C-Path: A Public Private Partnership

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs



- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools

C-Path Consortia

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

Coalition Against Major Diseases
Focusing on diseases of the brain

Coalition For Accelerating Standards and Therapies
Data standards

Critical Path for Parkinson's Consortium
Enabling clinical trials in Parkinson's Disease

Critical Path to TB Drug Regimens
Accelerating the development of TB drug regimens and diagnostics

Duchenne Regulatory Science Consortium
Duchenne Muscular Dystrophy

International Neonatal Consortium
Neonatal clinical trials

Multiple Sclerosis Outcome Assessments Consortium
Drug Effectiveness in MS

Polycystic Kidney Disease Outcomes Consortium
New imaging biomarker for PKD

Patient-Reported Outcome Consortium
Assessing treatment benefit

Electronic Patient-Reported Outcome Consortium
Electronic capture of treatment benefit

Predictive Safety Testing Consortium
Drug safety

Pediatric Trials Consortium
Developing effective therapies for children

- ✓ Biomarkers
- ✓ Clinical outcome assessment instruments
- ✓ Clinical trial simulation tools
- ✓ Data standards
- ✓ In vitro tools

C-Path Collaborators

Industry

- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Santhera Pharmaceuticals
- Sarepta Therapeutics
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

Nonprofit Research Organizations

- Alzheimer's Association
- Alzheimer's Drug Discovery Foundation
- Alzheimer's Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children's Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson's UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer's
- CHDI Foundation

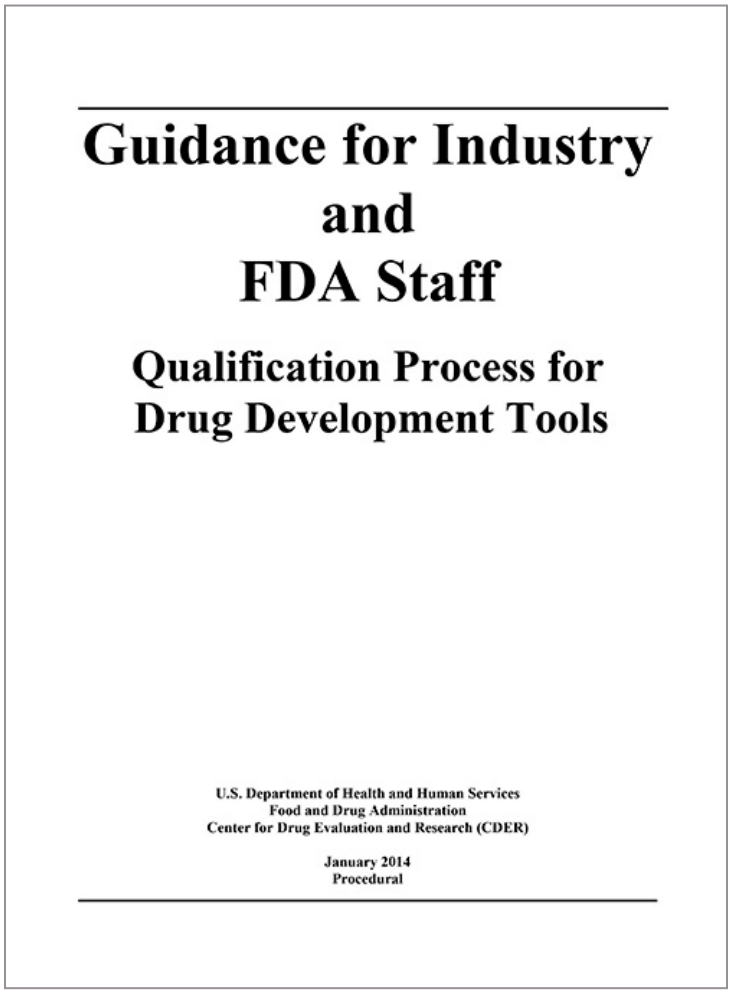
Government and Regulatory Agencies

- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

Academic Institutions

- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University

FDA and EMA Qualification:
A Formal Process of Review and Acceptance

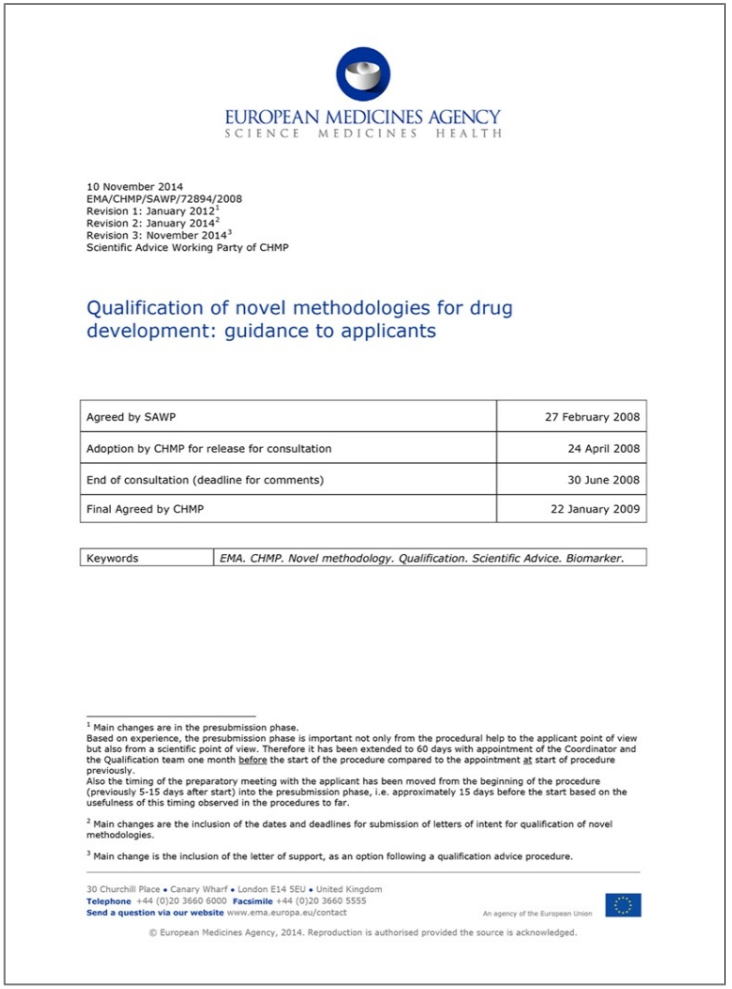


Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

[1] Main changes are in the presubmission phase.
Based on experience, the presubmission phase is important not only from the procedural help to the applicant point of view but also from a scientific point of view. Therefore it has been extended to 60 days with appointment of the Coordinator and the Qualification team one month before the start of the procedure compared to the appointment at start of procedure previously.
Also the timing of the preparatory meeting with the applicant has been moved from the beginning of the procedure (previously 5-15 days after start) into the presubmission phase, i.e. approximately 15 days before the start based on the usefulness of this timing observed in the procedures to far.

[2] Main changes are the inclusion of the dates and deadlines for submission of letters of intent for qualification of novel methodologies.

[3] Main change is the inclusion of the letter of support, as an option following a qualification advice procedure.

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Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

C-Path Core Competencies

- Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment
- Comprehensive modeling & simulation programs
- Novel *in vitro* tools to expedite proof-of-concept
- Outcome assessment instrument development
- Clinical data standards development
- Secure data management, standardization, curation, database development
- Forming and managing large international teams as well as collaborative ventures across organizations (e.g., IMI, FNIH)

Biomarker Qualification

- **Definition**: A conclusion that, within a carefully and specifically stated "context of use," the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

- **Context of Use (COU)**: A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development

- Dr. Shashi Amur (FDA) will cover this in detail

Biomarker Qualification

- Publicly Announced Decision from FDA regarding acceptance of utility of biomarker within the defined context of use, accompanied by a draft guidance on the use of that/those biomarker(s)
- Publicly Announced Decision from EMA regarding acceptance of utility of biomarker within the defined context of use but without a guidance/guideline

- **VALUE PROPOSITION FOR QUALIFYING BIOMARKERS**:
  - Sponsors of drug development programs have confidence to incorporate biomarkers into their trial designs
  - Regulatory authorities have confidence to rely on biomarkers during their review process

Potential Context of Use Statements for AAbs Regulatory Qualification

- **INITIAL QUALIFICATION GOAL**:
  - Multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, or three variants (R, W or Q on position 325) of the ZnT8 transporter are a prognostic marker for disease progression in presymptomatic type 1 diabetes (T1D).
  - The beta cell autoantibodies may be used as an enrichment factor for the design of clinical trials and identification of subjects likely to benefit from interventions being developed for delay of the clinical onset or prevention of symptomatic type 1 diabetes.

- **ULTIMATE GOAL IN THE FUTURE**:
  - Prevention of the appearance of one or multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, and/or ZnT8 can be used as an endpoint in clinical trials as a surrogate marker for prevention of type 1 diabetes.

Consortium Will Focus on Regulatory Qualification

- **Letters of Intent to U.S. FDA and to EMA**
- **Developing Proposed Research Plan to gain necessary evidence**
  - Assessing and gaining access to available data on biomarkers
  - Meetings with regulatory authorities
- **Executing Research Plan**
  - Securing aggregated data set in C-Path data platform
  - Conducting necessary analyses
- **Preparing final qualification submission package for regulatory authorities**

What We Will Not Do

- **Biomarker discovery** – rather, we focus on biomarker development when a biomarker is close enough to being "regulatory ready"
- **Focus only on writing manuscripts** – rather, we aim for regulatory focused documents to push toward our deliverable to qualify appropriate, evidence-based biomarkers and then we publish accordingly
- **Fund independent research** – rather, we work in a collaborative manner, being good stewards of monetary and in-kind contributions to achieve clearly stated objectives to qualify biomarkers

Key Success Factors for Data Sharing

- Address Range of Objectives for Data Sharing
- Clear Quality Criteria
- Consistent and Transparent Data Process
- Maximize Data Utility Through Standardization
- Ongoing Curation, Validation and Reporting

Data Sharing

- **Context of use is key**
- **Some examples below**
- **Use cases are not exclusive**

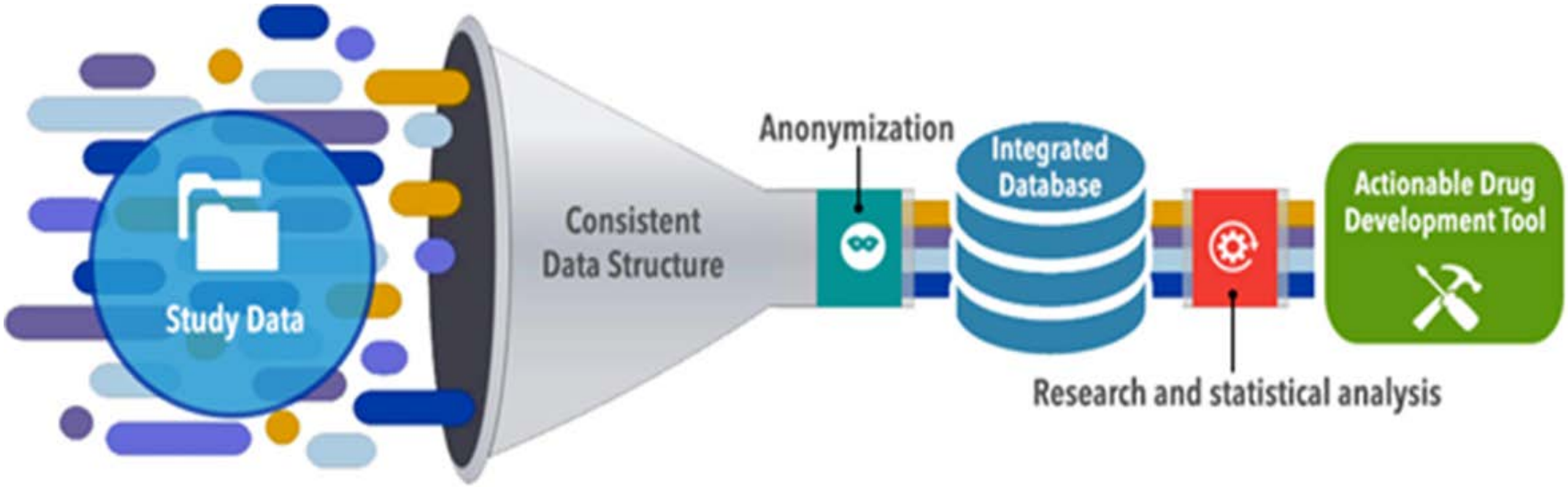
Use case	Examples
Specific project objective	• Biomarker qualification • Clinical Outcome Assessment qualification • Disease progression model / trial simulation tools
Accelerate research in a therapeutic area	• Research challenges to accelerate discovery (crowdsourcing)
Clinical data transparency	• ClinicalStudyDataRequest.com

Data Capability & Safeguards

Establish a pooled, standardized, secure database of clinical trial data

- **Range of objectives for data sharing drives differences in implementation**
- **Competing requirements need to be addressed**
  - Need to comply with all applicable regulations
  - Need to protect patient privacy (HIPAA and laws in other countries)
  - Need to respect sponsor confidential information and intellectual property
  - Need to optimize utility of shared data
- **Complicated by access and use of data from multiple sources**
- **A wide range of data types need to be handled**
  - Clinical trial data, observational study data, registry data
  - Comprising genotypic, phenotypic, treatment, outcome data

C-Path Data Mapping and Integration Process

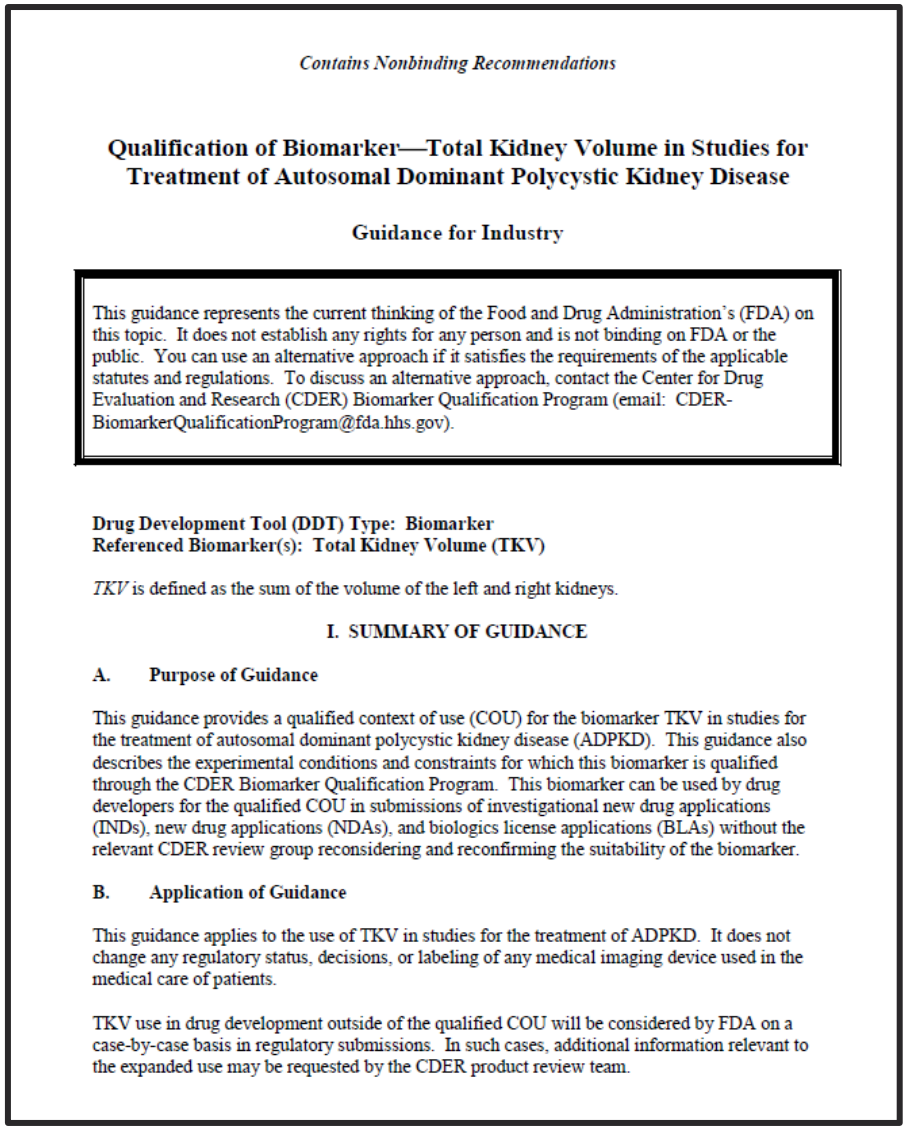


Data as contributed

Master Standardized Datasets

Analysis Datasets

PKDOC – FDA Qualification for TKV



Contains Nonbinding Recommendations

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration's (FDA) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Total Kidney Volume (TKV)

TKV is defined as the sum of the volume of the left and right kidneys.

I. SUMMARY OF GUIDANCE

A. Purpose of Guidance

This guidance provides a qualified context of use (COU) for the biomarker TKV in studies for the treatment of autosomal dominant polycystic kidney disease (ADPKD). This guidance also describes the experimental conditions and constraints for which this biomarker is qualified through the CDER Biomarker Qualification Program. This biomarker can be used by drug developers for the qualified COU in submissions of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker.

B. Application of Guidance

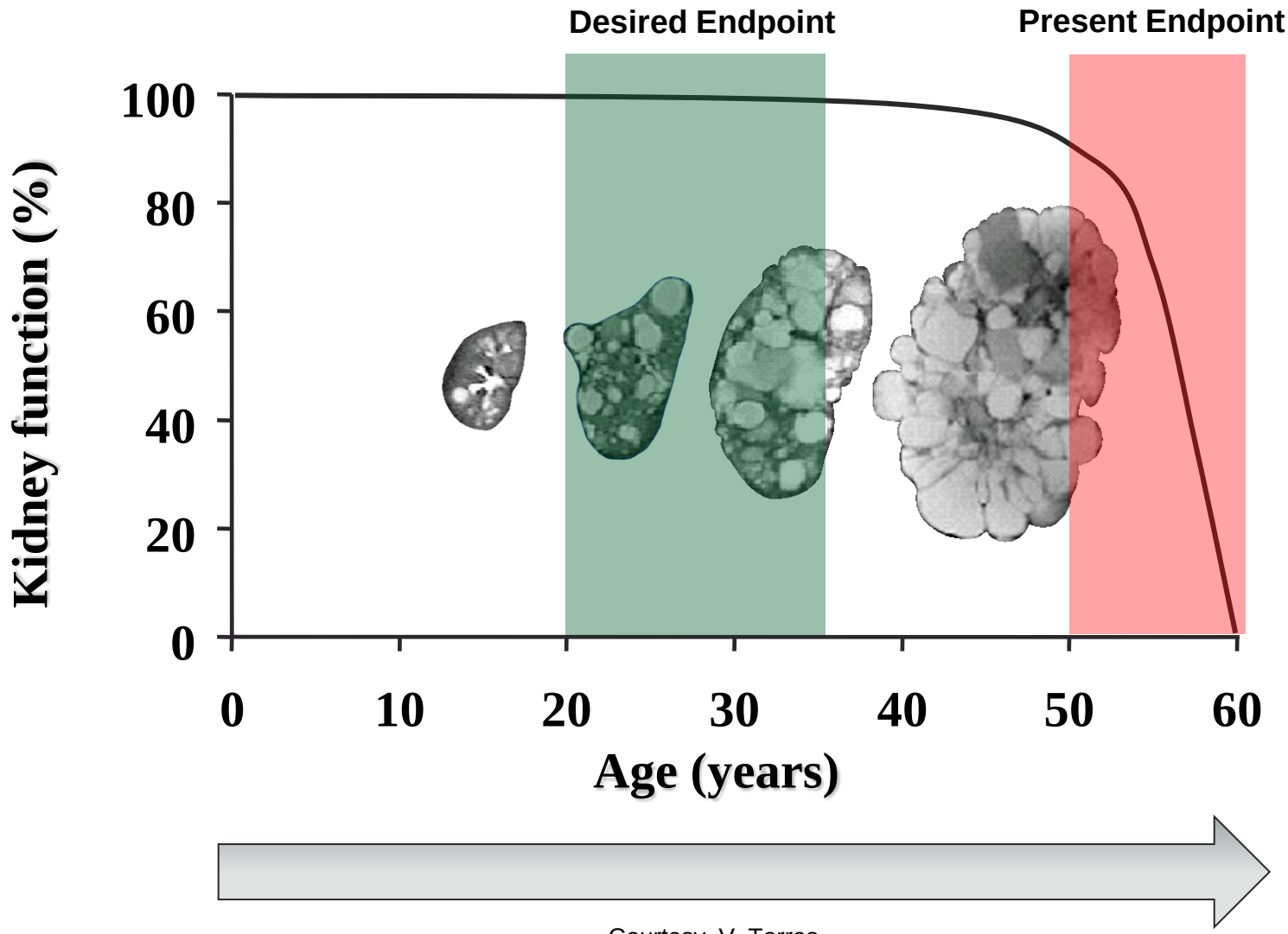
This guidance applies to the use of TKV in studies for the treatment of ADPKD. It does not change any regulatory status, decisions, or labeling of any medical imaging device used in the medical care of patients.

TKV use in drug development outside of the qualified COU will be considered by FDA on a case-by-case basis in regulatory submissions. In such cases, additional information relevant to the expanded use may be requested by the CDER product review team.

"guidance to C-Path's Polycystic Kidney Disease Outcomes Consortium (PKDOC) for total kidney volume (TKV) as a prognostic biomarker to select patients for clinical trials of new therapies for Autosomal Dominant Polycystic Kidney Disease (ADPKD). "

Dr. Shashi Amur (FDA) will cover this in detail

Changing the Paradigm for Measuring Disease Progression of PKD



Courtesy V. Torres

FDA Qualifications of Drug Development Tools

C-Path Consortia have achieved two qualifications by the FDA:

- PKDOC – Imaging of total kidney volume (TKV) as prognostic enrichment factor for clinical trials in polycystic kidney disease.
- PSTC - Final conclusions on the pilot joint European Medicines Agency/U.S. Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

Fit-For-Purpose accomplishments:

- CAMD - A novel, data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease

C-Path's ongoing biomarker qualification programs:

- Drug safety biomarkers for the kidney, liver, pancreas and testes
- Prognostic biomarkers for patient stratification

EMA Qualifications of Novel Methodologies for Medicine Development

C-Path Consortia have achieved four qualifications by the EMA:

- CPTR - In-vitro hollow fiber system model of tuberculosis (HFS-TB)
- CAMD - A novel, data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease
- CAMD - Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer's disease
- PSTC - Final conclusions on the pilot joint European Medicines Agency/U.S. Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers
- PKDOC – Imaging of total kidney volume (TKV) as prognostic enrichment factor for clinical trials in polycystic kidney disease.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

FDA Letters of Support

C-Path consortia have received seven of the eleven Letters of Support issued by the FDA:

Requester	Biomarker(s)	Area(s) for Use in Drug Development	Issuance Date with Link to Letter of Support	Requester Contact
Critical Path Institute's (C-Path) Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development	8/20/2014: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, PSTC, Skeletal Muscle Working Group (SMWG)	Serum and Plasma Biomarkers: Myosin Light Chain 3 (Myl3), Skeletal Muscle Troponin I (sTNI), Fatty Acid Binding Protein 3 (FABP3), Creatine Kinase, Muscle Type (CK-M, the Homodimer CK-MM)	Early Clinical Drug Development	1/22/2015: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, Coalition Against Major Diseases Consortium (CAMD)	Cerebral Spinal Fluid (CSF) Analyte Biomarkers: $A\beta_{1-42}$, Total tau, Phosphotau	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	2/26/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Magnetic Resonance Imaging Biomarker: Low Baseline Hippocampal Volume	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	3/10/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Parkinson's Disease Clinical Trials	3/16/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, Polycystic Kidney Disease (PKD) Outcomes Consortium	MRI, Computerized Tomography (CT), or Ultrasound (US) Biomarker: Total Kidney Volume (TKV)	Exploratory Prognostic Biomarker for Enrichment in Autosomal Dominant Polycystic Kidney	4/23/2015: Letter of Support (PDF)	Refer to Polycystic Kidney Disease Outcomes Consortium Web Site
The Safer and Faster Evidence-based Translation Consortium (SAFE-T)	Cytokeratin 18 (CK-18), Total and Hyperacetylated High Mobility Group Protein B1 (HMGB1), Osteopontin, and Macrophage Colony-Stimulating Factor 1 Receptor (CSF1R)	Exploratory Monitoring Biomarkers for Use in Drug Development as a Clinical Safety Assessment of the Risk of Drug-induced Liver Injury (DILI) Progression	7/25/2016: Letter of Support (PDF)	Drs. Gerd Kullak-Ublick, Sif Ormarsdottir, John-Michael Sauer or Douglas Keller or view either the Critical Path Institute Website or the IMI SAFE-T Consortium Website

http://www.fda.gov/drugs/developmentapprovalprocess/ucm434382.htm

EMA Letters of Support

C-Path consortia have received four of the twelve Letters of Support issued by the EMA :

- PSTC – Skeletal Muscle Injury Biomarkers
- PSTC – Translational Drug-Induced Kidney Injury Biomarkers
- PSTC –Translational Drug-Induced Liver Injury Biomarkers
- PD – Clinical Trials Enrichment Tool Using Molecular Imaging of the Dopamine Transporter Biomarker

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

EMA/FDA Letters of Support

Dual EMA and FDA Letters of Support for DILI (October 2016):

IMI SAFE-T AND C-PATH PSTC OBTAIN REGULATORY SUPPORT FOR NEW LIVER SAFETY BIOMARKERS

US FDA and EMA Letters of Support Pave the Way for Clinical Qualification

The Innovative Medicines Initiative (IMI) SAFE-T (Safer and Faster Evidence Based Translation) Consortium and Critical Path Institute (C-Path) Predictive Safety Testing Consortium (PSTC) announced today that the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each issued a Biomarker Letter of Support for new liver safety biomarkers investigated by the SAFE-T Drug-Induced Liver Injury Work Package and the PSTC Hepatotoxicity Working Group. The Drug-Induced Liver Injury Network (DILIN) in the US, an expert network established by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), contributed their expertise to the research, as well as rare samples from individuals with severe liver injury.

Thank you

www.c-path.org

CRITICAL PATH INSTITUTE

FDA

FLINN FOUNDATION

SCIENCE foundation ARIZONA
Innovation at Work

C-Path Accomplishments

- ✓ First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
- ✓ First imaging biomarker for trial enrichment qualified by the EMA (for Alzheimer's disease)
- ✓ First imaging biomarker for trial enrichment qualified by the FDA and EMA (for Polycystic Kidney Disease)
- ✓ First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer's disease), and additional standards for TB, PD, PKD, MS, and Influenza
- ✓ First drug-disease-trial model for AD endorsed by the FDA & EMA
- ✓ First Drug Development Tool for TB Qualified by EMA and included in FDA Guidance for TB Drug Development

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

QUALIFICATION OF NOVEL BIOMARKERS IN TYPE ONE DIABETES/CHALLENGES AND OPPORTUNITIES
TYSONS CORNER, VA
NOVEMBER 7, 2016

FDA'S BIOMARKER QUALIFICATION PROGRAM

Shashi Amur, Ph.D.

Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

OVERVIEW

- DDT Qualification
- Biomarkers
- Biomarkers in Drug Development
- Biomarker Development and Qualification
- Role of Consortia in Biomarker Development
- Summary

DRUG DEVELOPMENT TOOLS (DDT) QUALIFICATION AT CDER

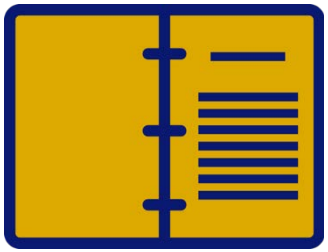
Clinical Outcome Assessments

Animal Models (Animal Rule)

Biomarkers

DDTs are methods, materials, or measures that aid drug development

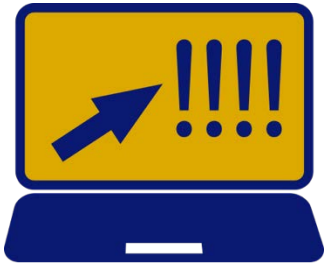
DDT QUALIFICATION AT CDER, FDA



Guidance for Industry and FDA Staff:

Qualification Process for Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf



Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

BIOMARKER

"Biomarker," or "biological marker," generally refers to a measurable indicator of some biological state or condition

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Types: Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

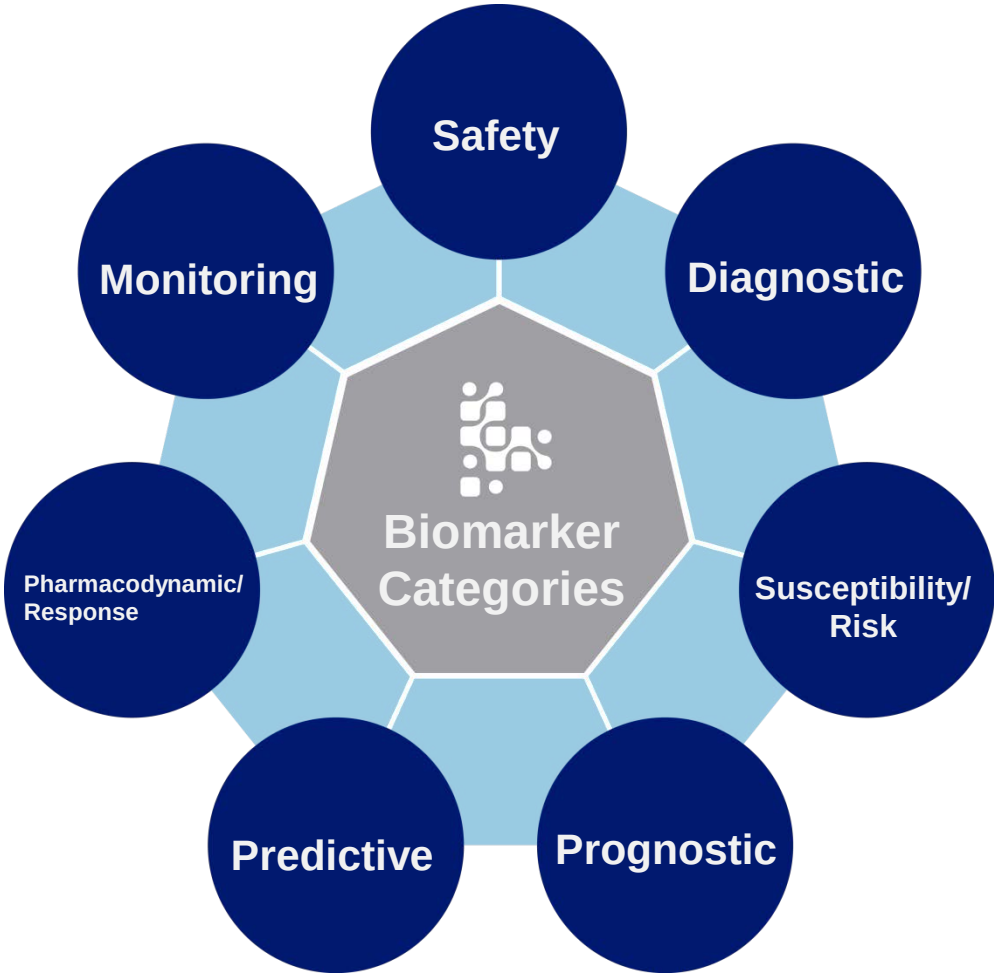
Examples:

- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)

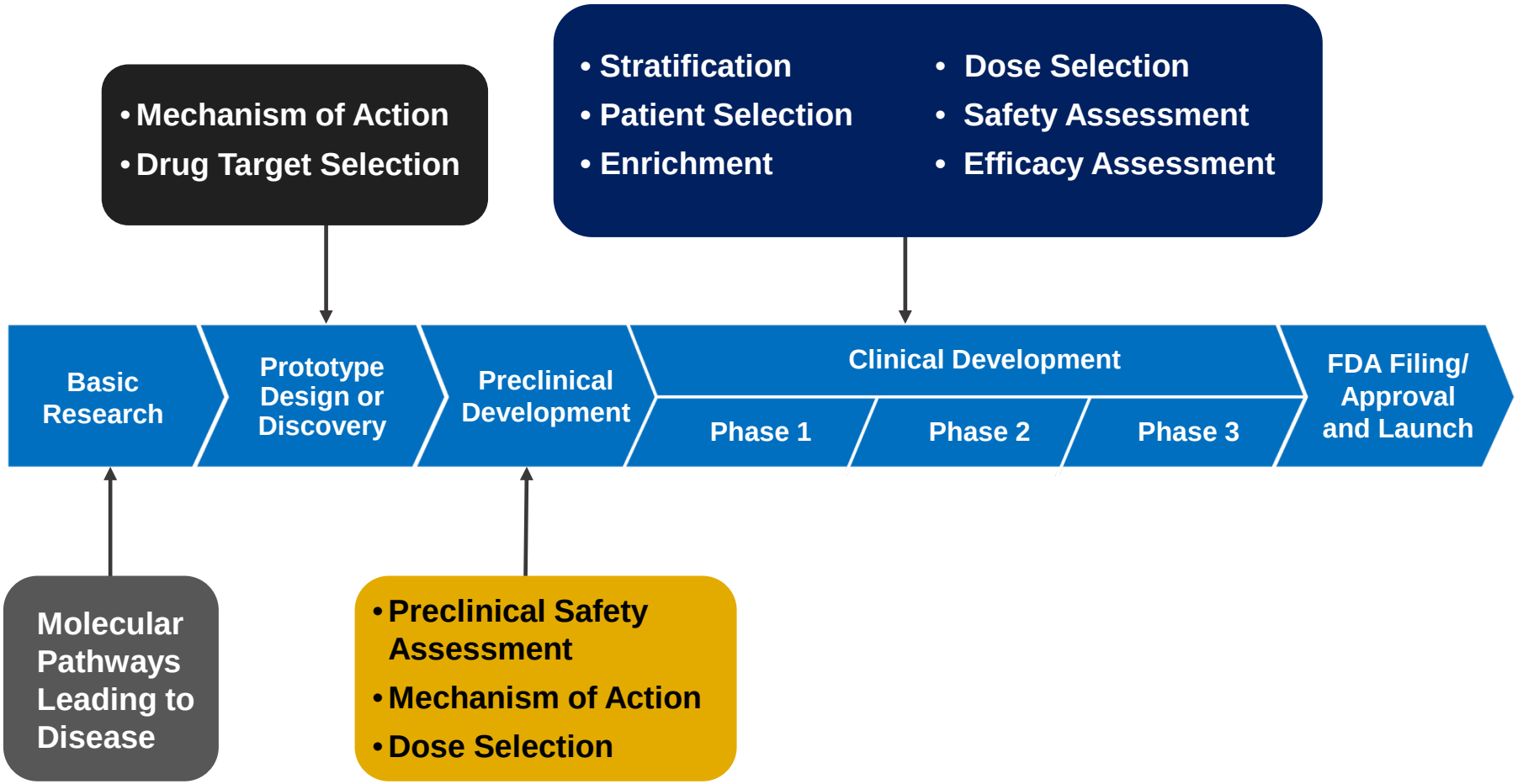
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/

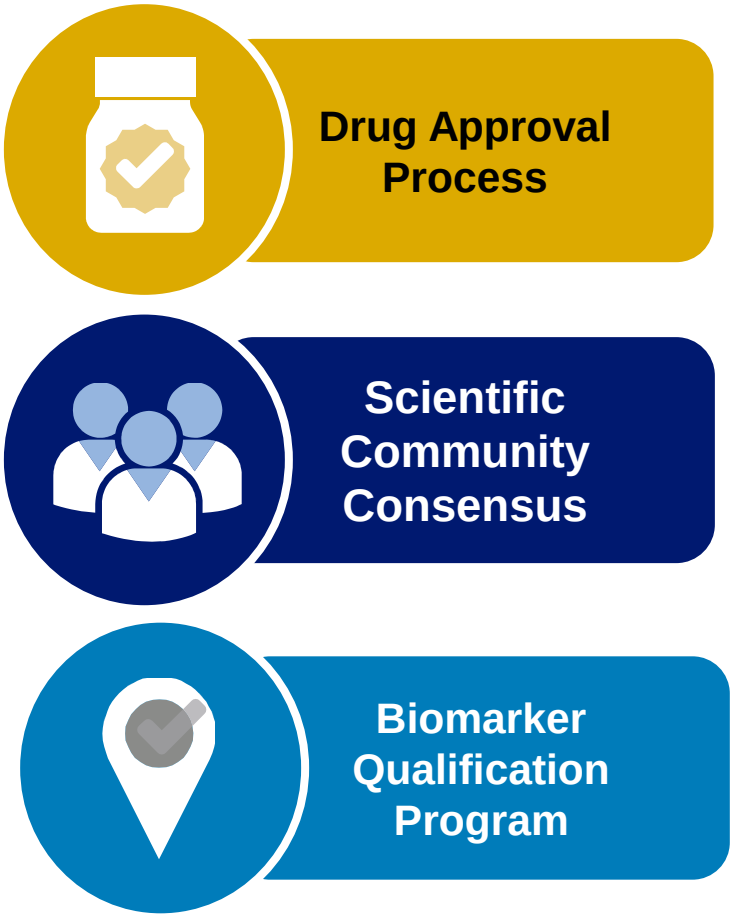
BIOMARKER CATEGORIES



EXAMPLES OF HOW BIOMARKERS ARE USED IN DRUG DEVELOPMENT



BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



DRUG APPROVAL (IND/NDA/BLA) APPROACH FOR BIOMARKER DEVELOPMENT

Drug Approval Process

Opportunities

- Focused use
- Data maintained by the biomarker developer

Challenges

- Biomarker data may not be generalizable
- Data aggregation
- Development costs
- Engagement with stakeholder groups
- Biomarker information may be available in drug labels and reviews upon approval

SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT

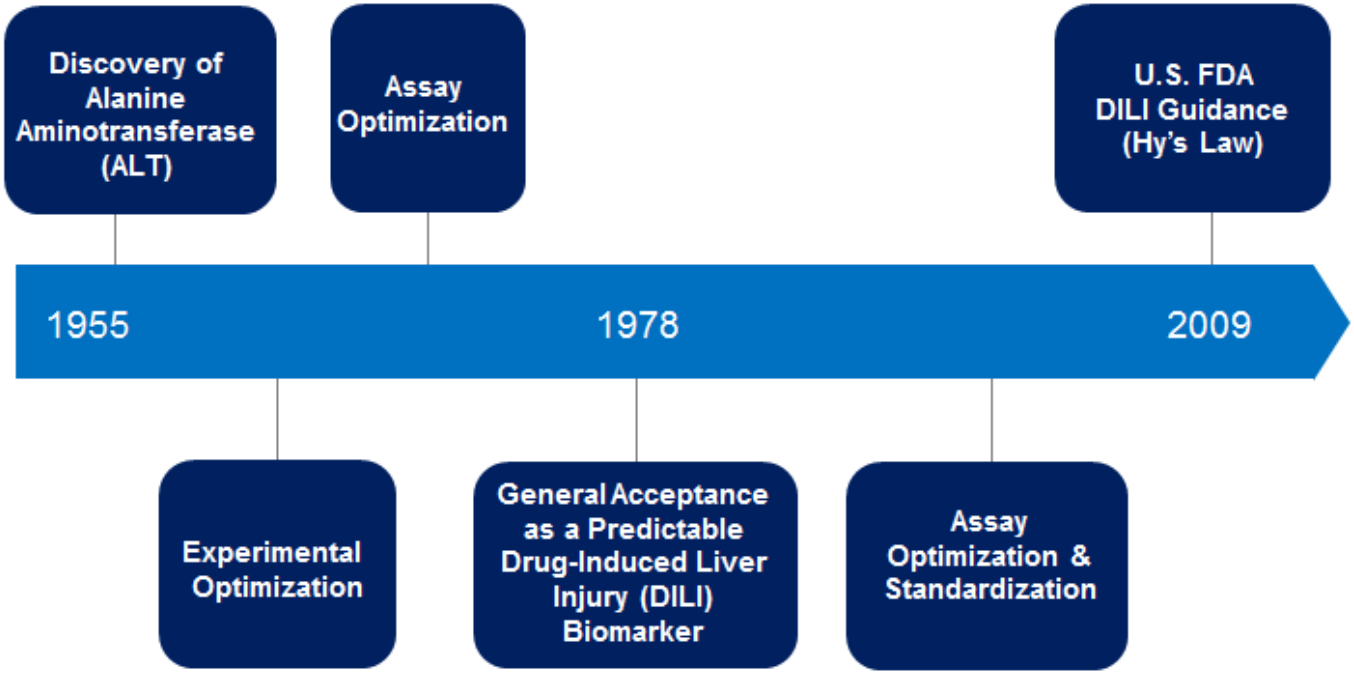
Opportunities

- Knowledge base of exploratory biomarker data in published literature
- Community input

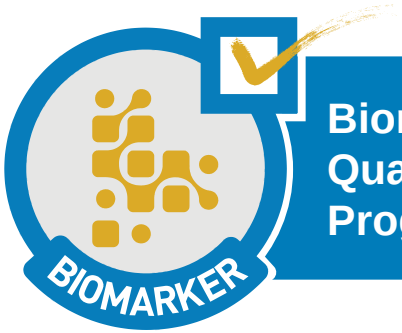
Challenges

- Data reproducibility
- Time to regulatory acceptance
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms

ESTABLISHMENT OF ALT AS AN ACCEPTED BIOMARKER FOR REGULATORY USE



BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT



Biomarker Qualification Program

Opportunities

- Context of use clearly established
- Pool resources and costs
- Engage outside experts
- Leverage stakeholder groups
- Public guidance with supporting reviews

Challenges

- Coordination of stakeholders
- Data may not be widely available
- Data sharing and aggregation

BIOMARKER QUALIFICATION (BQ)

Definition: A conclusion that, within a carefully and specifically stated "context of use," the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

Context of Use (COU): A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development

BIOMARKER QUALIFICATION: SUBMITTER ROADMAP

Stage 1: Initiation

Submit Letter of Intent (LOI)

FDA determines acceptability of LOI

Stage 2: Consultation and Advice

Submit briefing package

Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review

Submit full qualification package

FDA reviews package and makes yes/no decision to qualify

FDA drafts guidance document

Publication of Guidance

Draft guidance document posted to Federal Register for public comment

FDA publishes final guidance document

LIST OF FDA-QUALIFIED BIOMARKERS

General Area	Submitter(s)	Biomarker(s) Qualified for Specific Contexts of Use	Issuance Date with Link to Specific Guidance	Supporting Information
Nonclinical	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil Factor-3	4/14/2008: Drug-Induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)	9/22/2010: Drug-Induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	PJ O'Brien, WJ Reagan, MJ York, and MC Jacobsen	Serum/plasma biomarkers: Cardiac Troponins T (cTnT) and I (cTnI)	2/23/2012: Drug-Induced Cardiotoxicity Biomarkers	Reviews
Clinical	Mycoses Study Group	Serum/bronchoalveolar lavage fluid biomarker: Galactomannan	10/24/2014: Patient Selection Biomarker for Enrollment in Invasive Aspergillosis (IA) Clinical Trials	Reviews
Clinical	Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Plasma biomarker: Fibrinogen	7/6/2015; Prognostic Biomarker for Enrichment of Clinical Trials in Chronic Obstruction Pulmonary Disease (COPD)	Reviews
Clinical	Polycystic Kidney Disease Outcomes Consortium	Imaging biomarker: Total Kidney Volume (TKV)	8/17/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Autosomal Dominant Polycystic Kidney Disease	Reviews

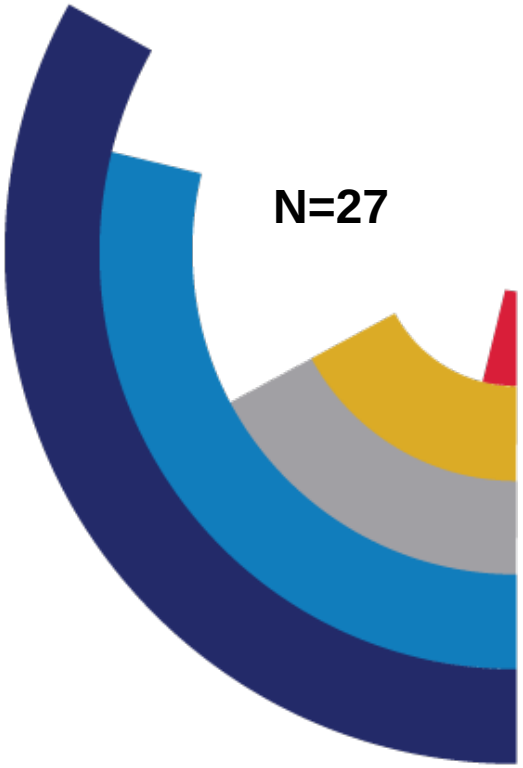
www.fda.gov/biomarkerqualificationprogram

BIOMARKER QUALIFICATION (BQ) SUBMISSIONS

Biomarker Qualification Program Metrics	
Number in Initiation Stage	7
Number in Consultation and Advice Stage	17
Number in Review Stage	4
Total Number of Active Projects	28
Number Qualified	6

From the Drug Development Tool (DDT) Qualification Projects at CDER, FDA:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm

TYPES OF SUBMISSIONS WE ARE SEEING FOR BIOMARKER QUALIFICATION



4% Monitoring

19% Patient Selection

22% Clinical Safety

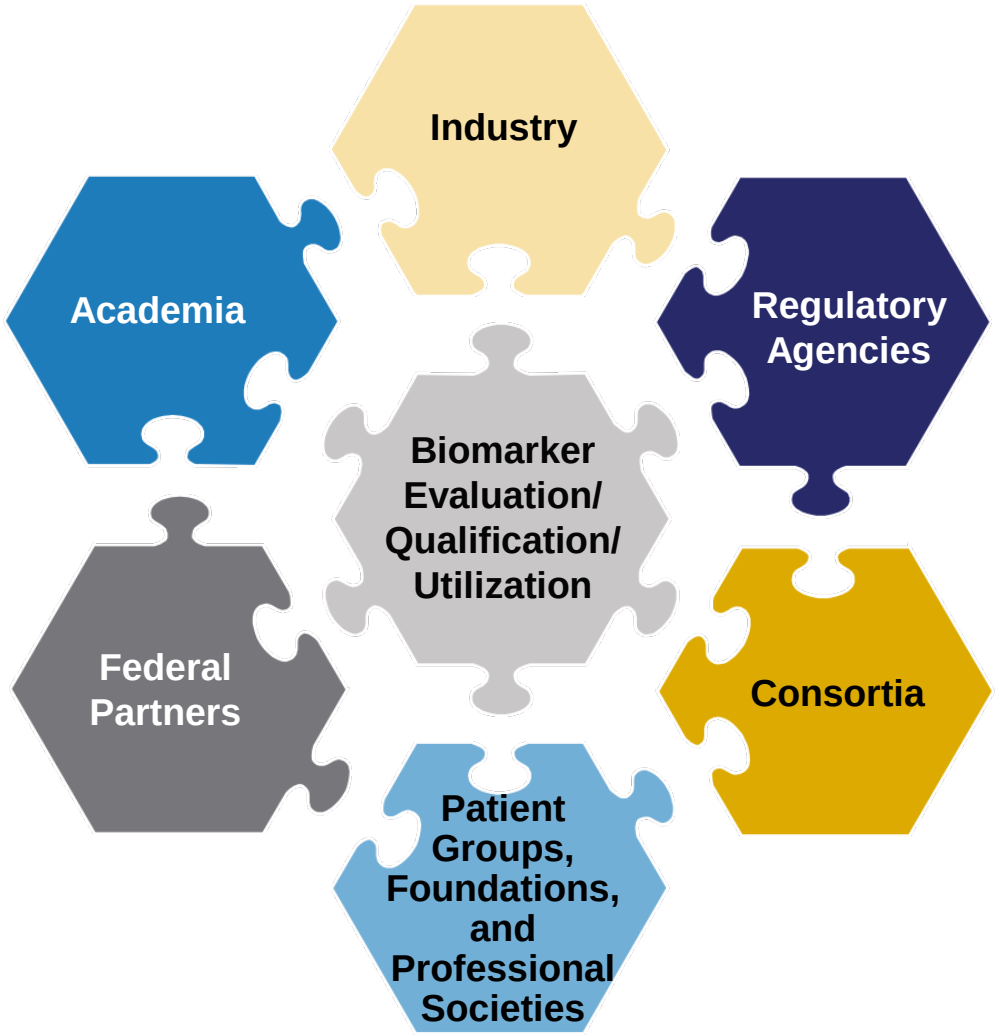
26% Preclinical Safety

30% Response

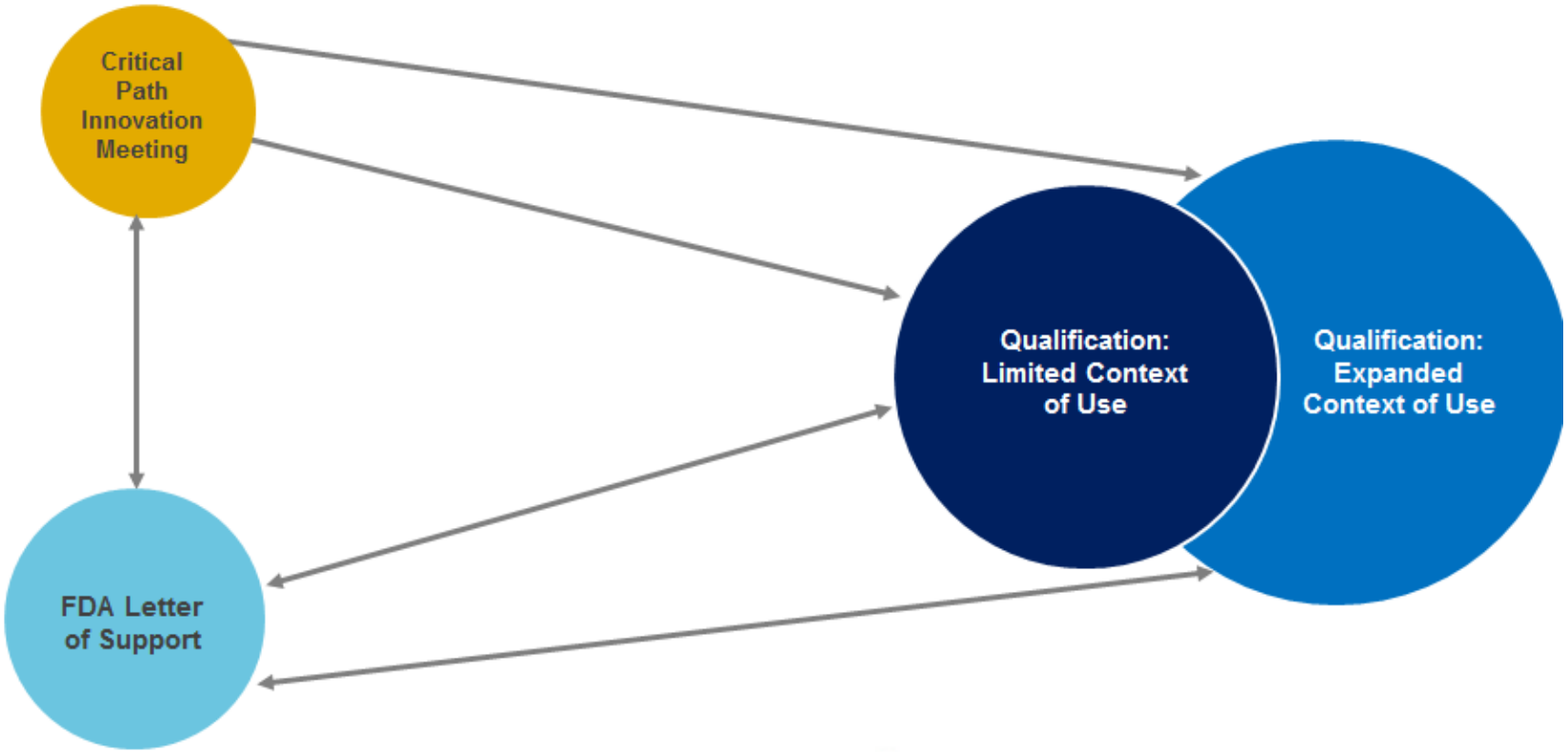
SOME ENABLERS FOR BIOMARKER DEVELOPMENT

- Data standards
- Data quality
- Data reproducibility
- Statistical considerations
- Assay/imaging considerations/validation
- Assay/imaging protocols
- Establishing cut points

STAKEHOLDERS IN BIOMARKER DEVELOPMENT



OPPORTUNITIES FOR ENGAGING FDA IN BIOMARKER DEVELOPMENT



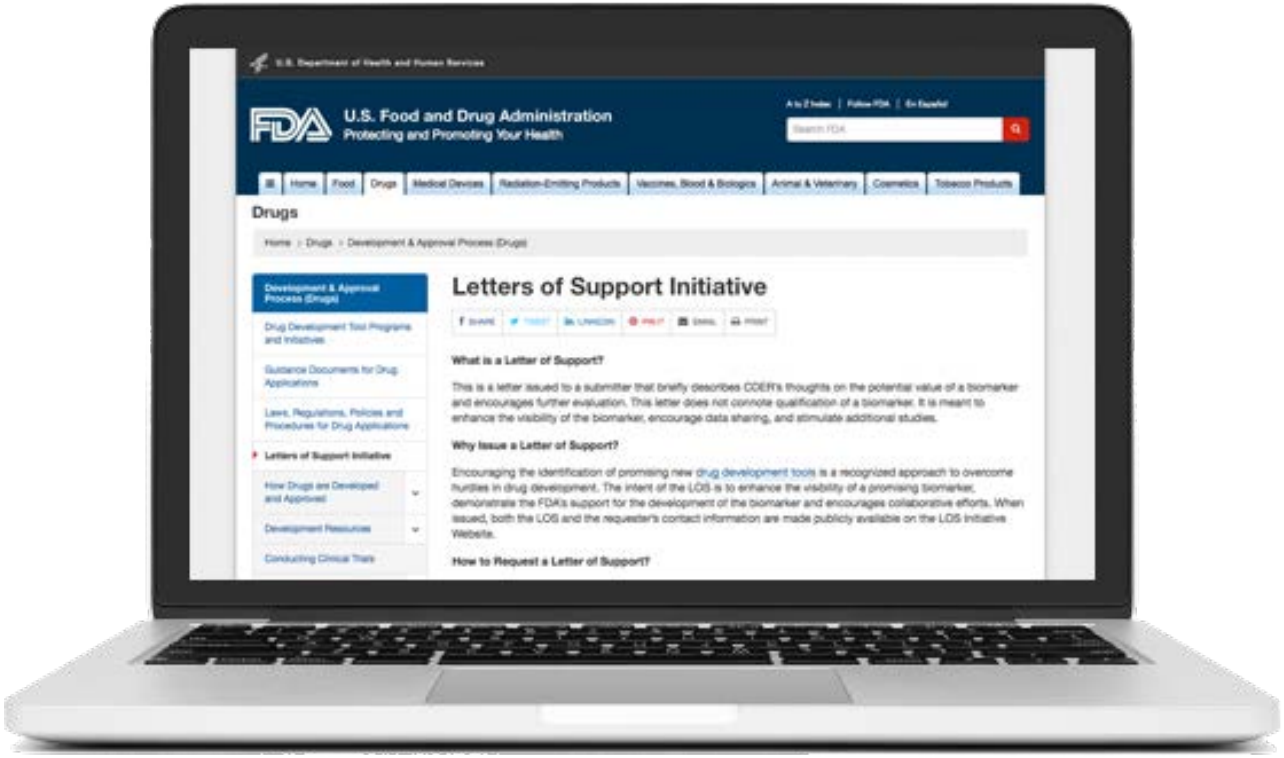
CRITICAL PATH INNOVATION MEETINGS

- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Nonbinding meeting
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods

Office of Translational Sciences
Critical Path Innovation Meeting

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformion/Guidances/UCM417627.pdf

LETTER OF SUPPORT



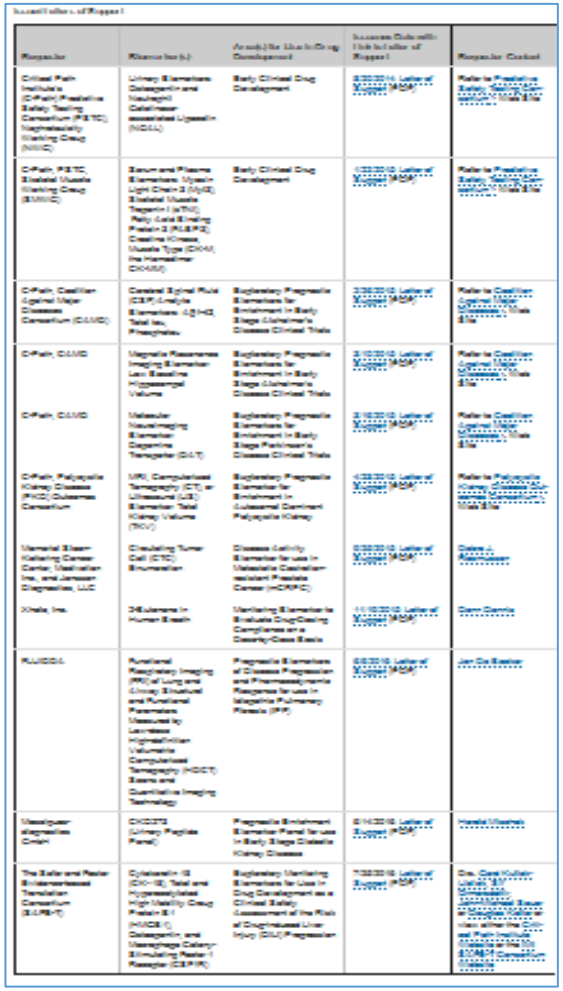
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

LETTER OF SUPPORT

- This is a letter issued to a requester that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation.

- **This letter does not connote qualification of a biomarker**. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

11 letters issued to date

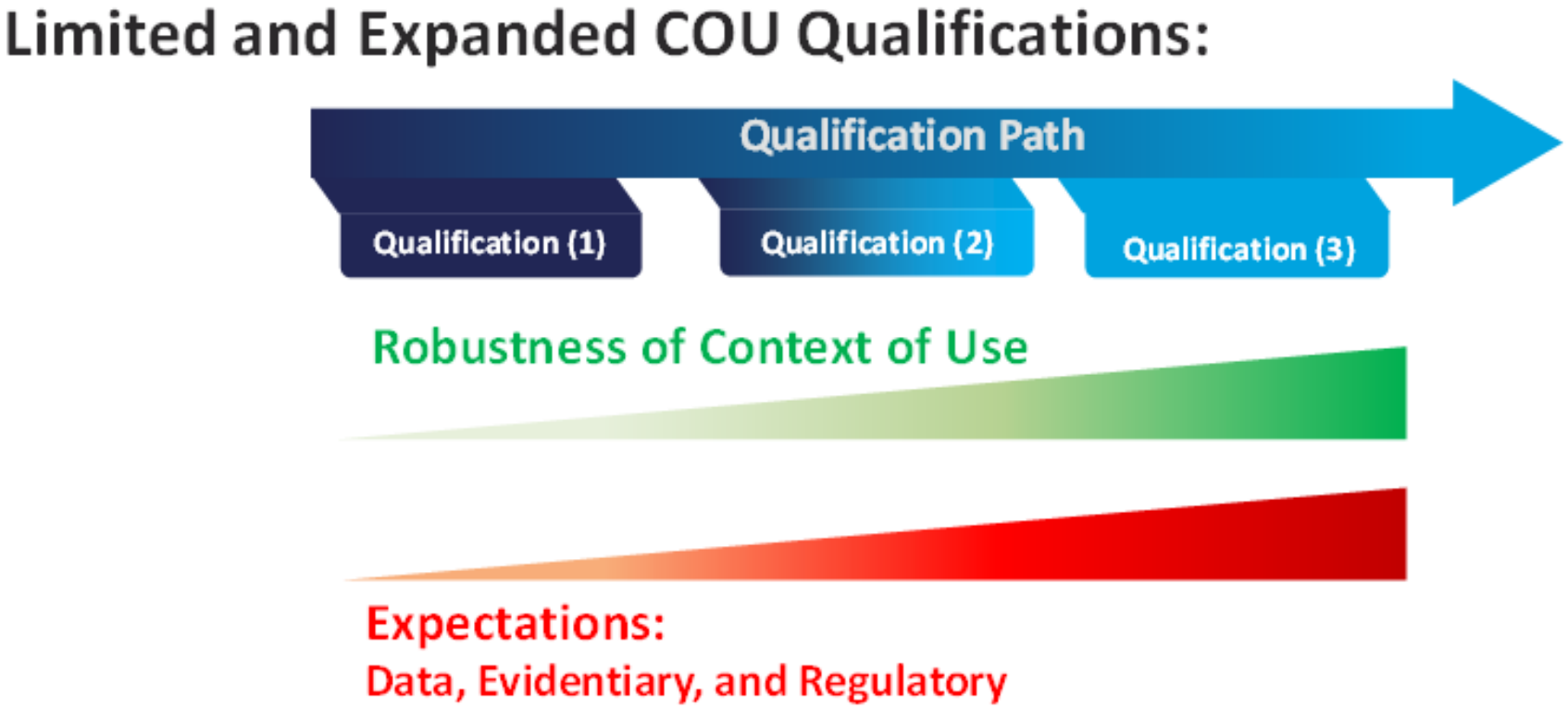


http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

LIMITED CONTEXT OF USE – BIOMARKER QUALIFICATION

CDER provides an avenue to qualify a biomarker for a "limited" context of use in order to expedite the integration of the biomarker in drug development and to possibly generate additional data that can help in qualifying the biomarker for the "expanded" context of use.

A CONTINUUM, NOT A DICHOTOMY…



Source: Slide Set from Dr. Martha Brumfield, President and CEO of Critical Path Institute

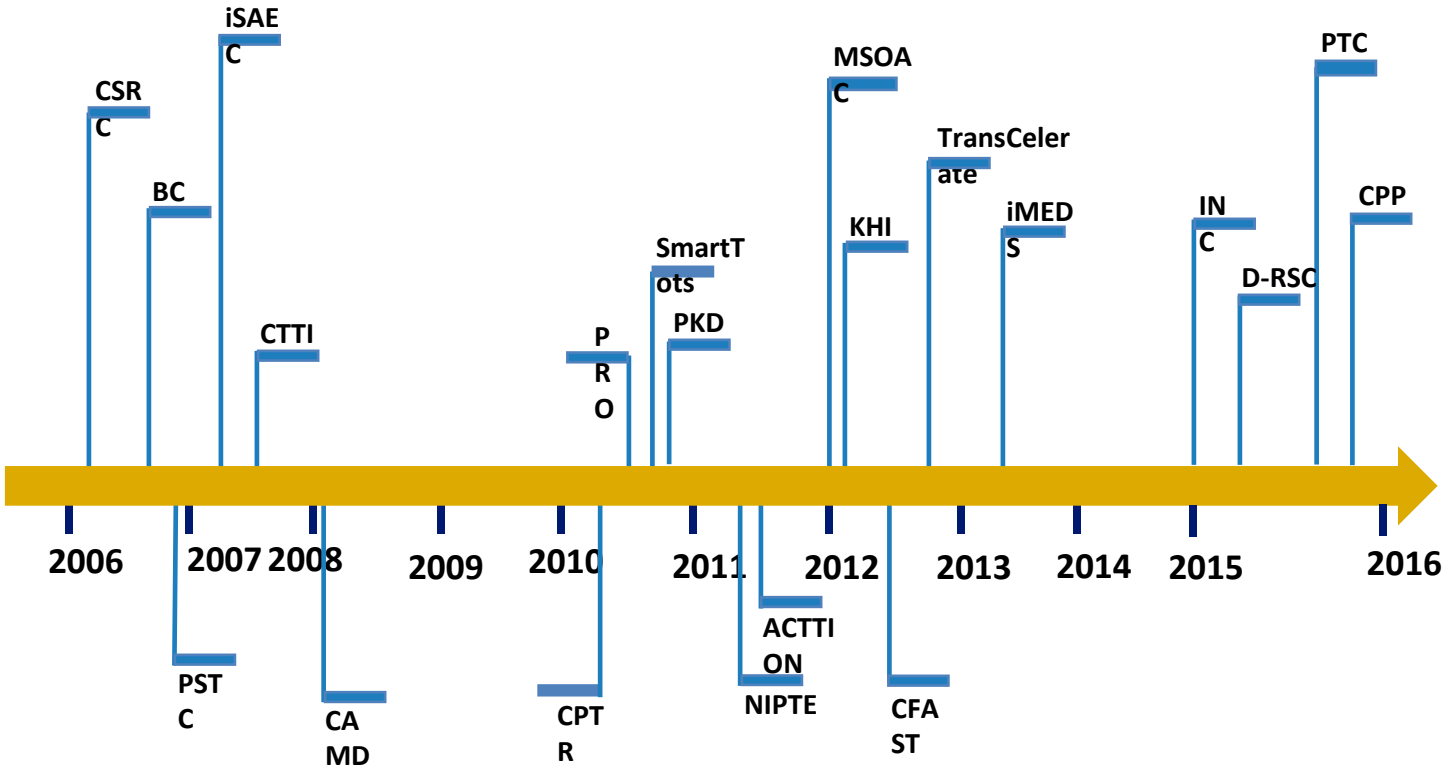
BIOMARKER QUALIFICATION SUBMITTERS

Organization	Number (N=28)	Percentage of Total BQ Submission
Consortia	19	68%
Diagnostics and Biotechnology	4	14%
Academia	3	11%
Contract research organizations	2	7%

Consortium: A group that is “formed to undertake an enterprise beyond the resources of any one member” (includes disease foundations)

Contract research organization (CRO): is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

Examples of Consortia



Cardiac Safety Research Consortium (**CSRC**), Biomarker Consortium (**BC**), Predictive Safety Testing Consortium (**PSTC)**, international Serious Adverse Event Consortium **(iSAEC),** Clinical Trials Transformation Initiative (**CTTI)**, Coalition Against Major Disease Consortium (**CAMD**), Critical Path to TB Drug Regimens (**CPTR**) Consortium, Patient Reported Outcomes (**PRO**) Consortium, Polycystic Kidney Disease Outcomes (**PKD**) Consortium, National Institute for Pharmaceutical Technology and Education (**NIPTE**), Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (**ACTTION**), Multiple Sclerosis Outcome Assessments Consortium (**MSOAC**), Kidney Health Initiative (**KHI**), Coalition For Accelerating Standards and Therapies (**CFAST**), Innovation in Medical Evidence Development and Surveillance (**iMEDS**) Program, International Neonatal Consortium (**INC**), Duchenne-Regulatory Science Consortium (**D-RSC**), Pediatric Trials Consortium **(PTC),** Critical Path for Parkinson's **(CPP)** Consortium**.**

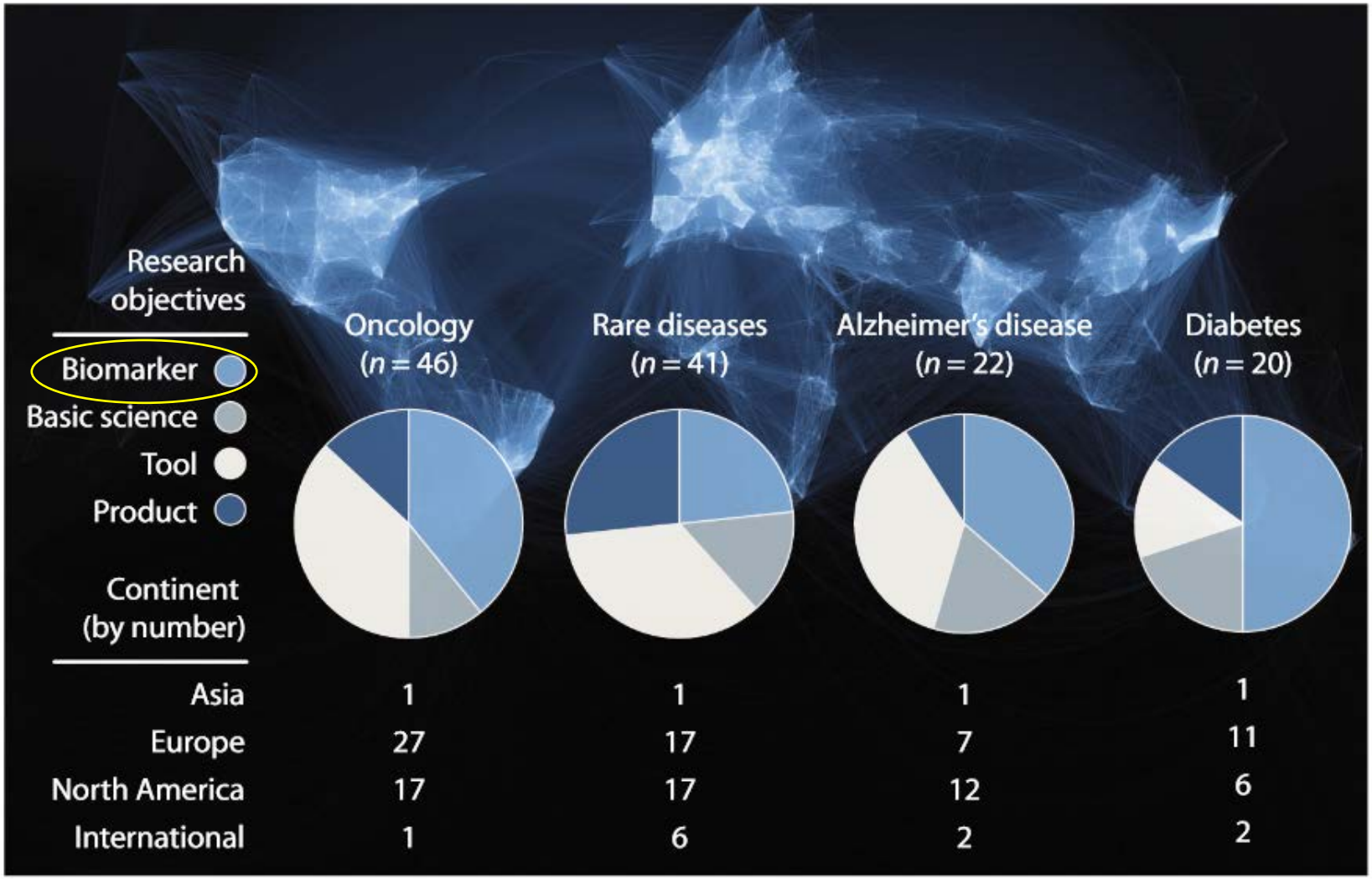
Consortia-pedia

http://consortiapedia.fastercures.org/about/

Consortia products

http://consortiapedia.fastercures.org/

Consortia By Disease Focus



Lim MD. Sci. Transl. Med. 6(242):242cm6. doi: 10.1126/scitranslmed.3009024 (2014)

Why are Consortia the Main Sources of BQ Submissions?

Consortia Provide

- A neutral environment to use collective expertise
- Opportunities to pool resources and share costs
- A governance structure for coordination of scientific research to develop biomarkers, leveraging resources and expertise
- Opportunities to bring in outside experts from industry/academia
- Opportunities to have a scientific liaison from government agencies such as FDA and NIH

Summary

- **BEST** (Biomarkers, Endpoints, and other Tools Resource) provides biomarker-relevant definitions, in an effort to harmonize biomarker terminology

- **Biomarker Qualification**
  - Submitter can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
  - No fees for submissions to the BQ program
  - Biomarker qualification is voluntary
  - Once qualified for a specific context of use, a biomarker can be used by drug developers for other applications

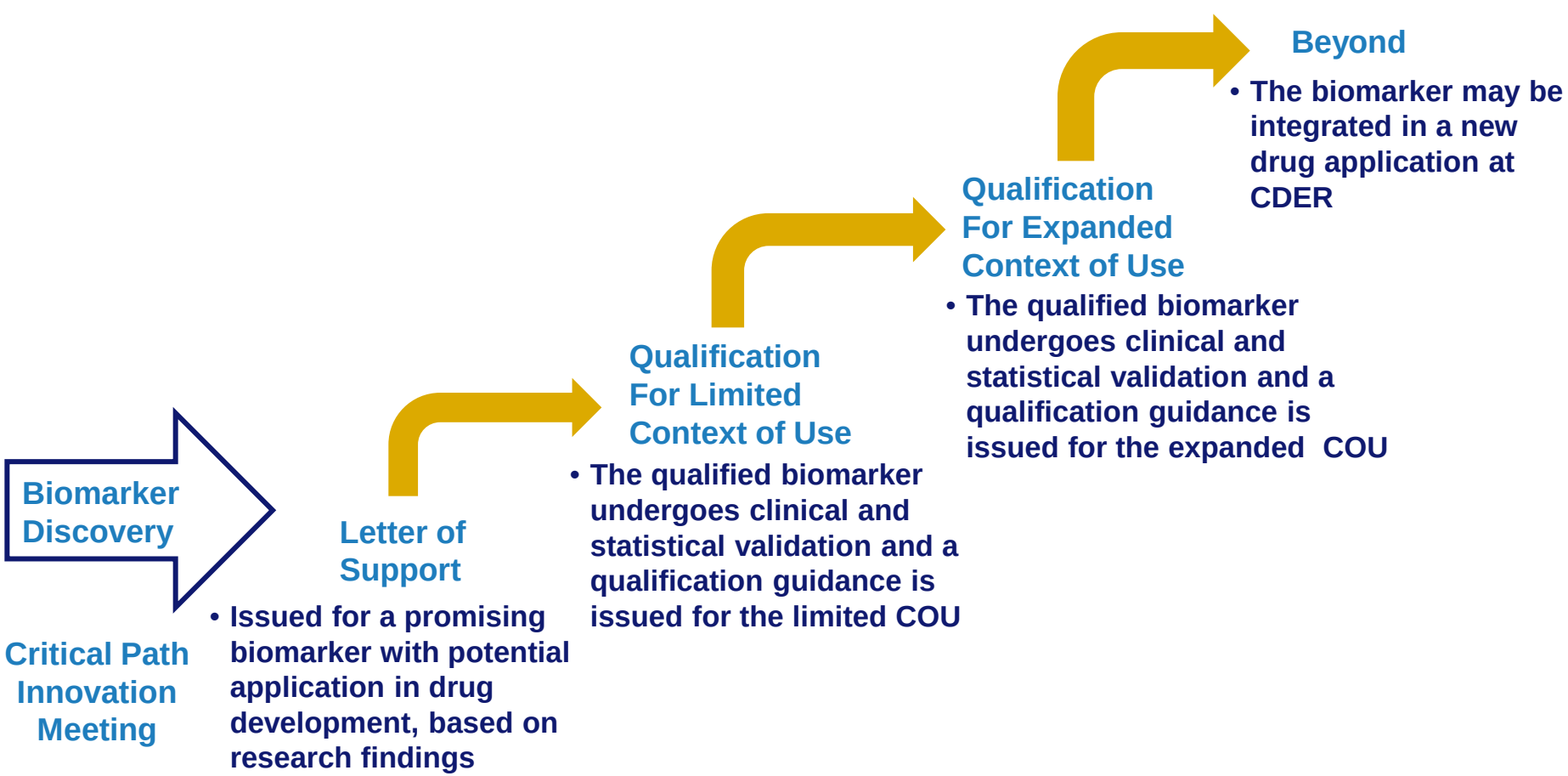
- **New FDA initiatives**, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development

- **Consortia** contribute the majority of submissions for biomarker qualification through coordination of collective expertise and shared resources

ACKNOWLEDGEMENTS

Janet Woodcock
ShaAvhrée Buckman-Garner
Suzie McCune
Chris Leptak
Marianne Noone
Sarmistha Sanyal
Kylie Haskins
Ru Chen

OPPORTUNITIES FOR CDER ENGAGEMENT IN BIOMARKER DEVELOPMENT



Break

Please return by 2:45 pm

Beta Cell Autoantibody Qualification Consortium

Steve Broadbent, COO

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Why Form a Consortium?

- Bring together industry, regulators, academic experts, and key societies/foundations to collaborate in areas of common interest
- Solve challenging problems difficult for one organization to tackle
- Engage FDA and EMA for advice to facilitate regulatory approval of new tools and methods
- Spread costs and risks to advance research in areas of unmet need
- Defined governance structure; scientific and project management leadership support, data acquisition and data platform support
- All leading to meaningful regulatory science deliverables

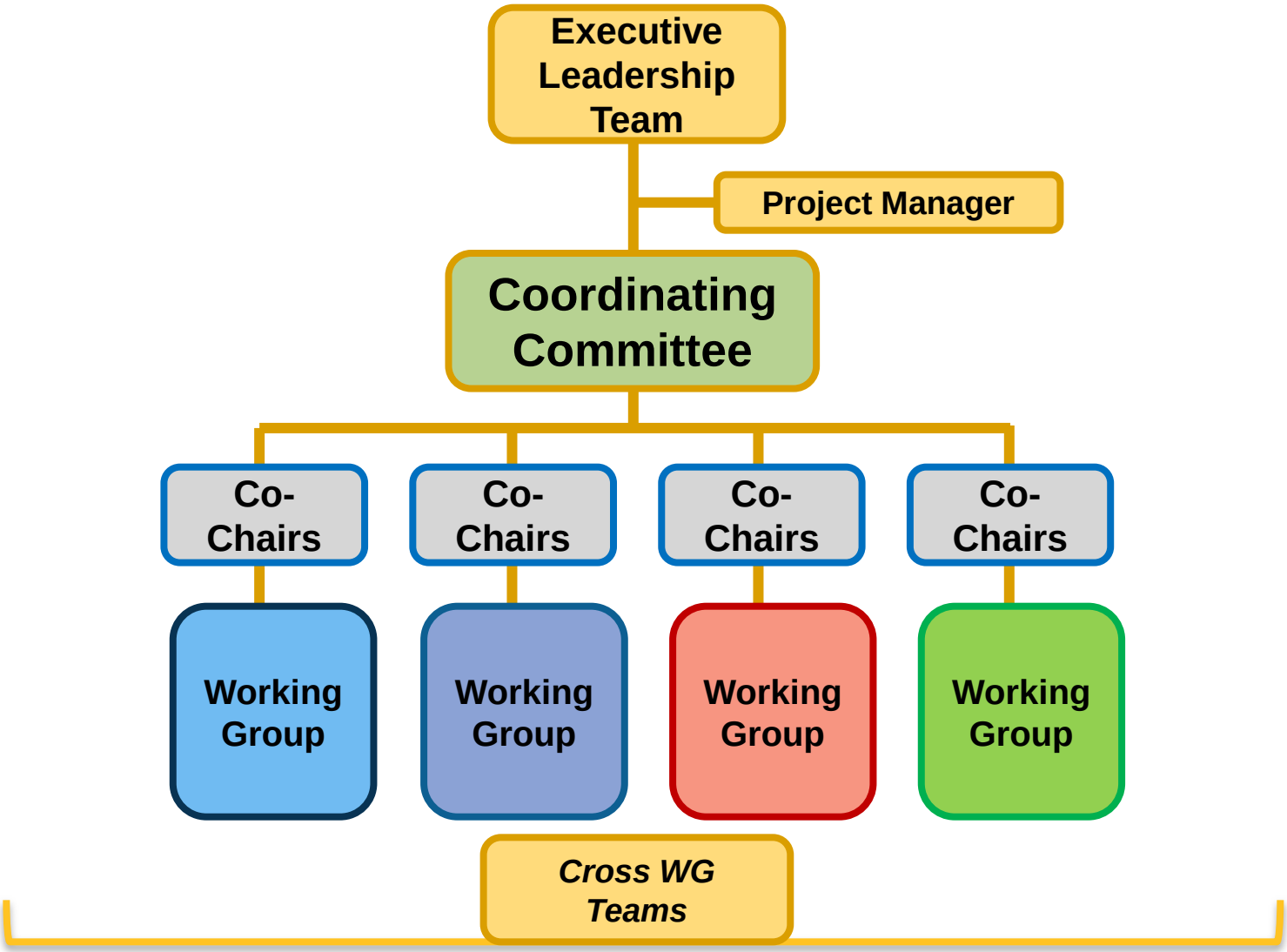
Membership Legal Agreement

- Initial Scope
- Responsibilities and Expectations of Members
- Governance
- Confidentiality
- Intellectual Property
- Publications and Publicity
- Fees
- Anti-Trust
- Anti-Corruption, Anti-Bribery
- Termination, Liability, Indemnification, etc.

Governance Model

- Executive Leadership Team consisting of C-Path executive director and co-director(s) from founding members
- Coordinating committee with representation for all members makes all significant decisions
- Separate Working Groups created to focus on each deliverable – led by a chair or co-chairs

Typical Governance Structure



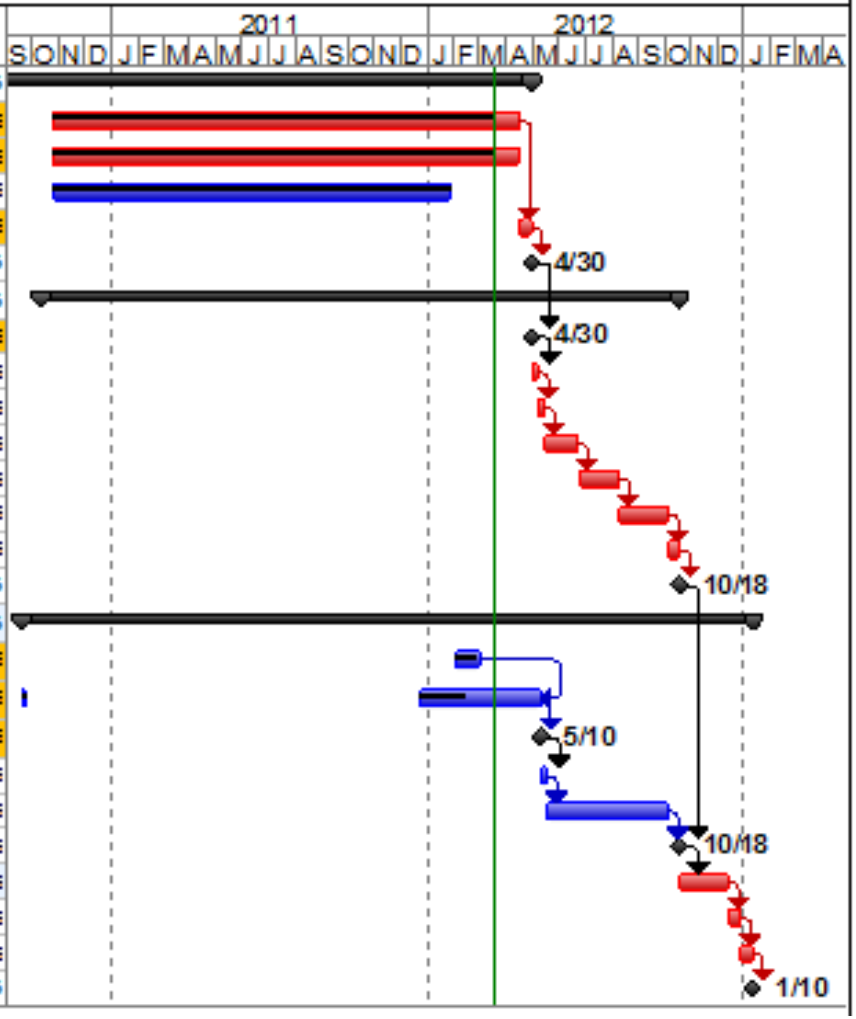
Project Management

- Written Goals and Deliverables
- Project Plan with Schedules
- Clear Tasks with Owners
- Tracking and Communicating
- Budgets and Finance
- Meetings and Workshops

Typical Project Schedule

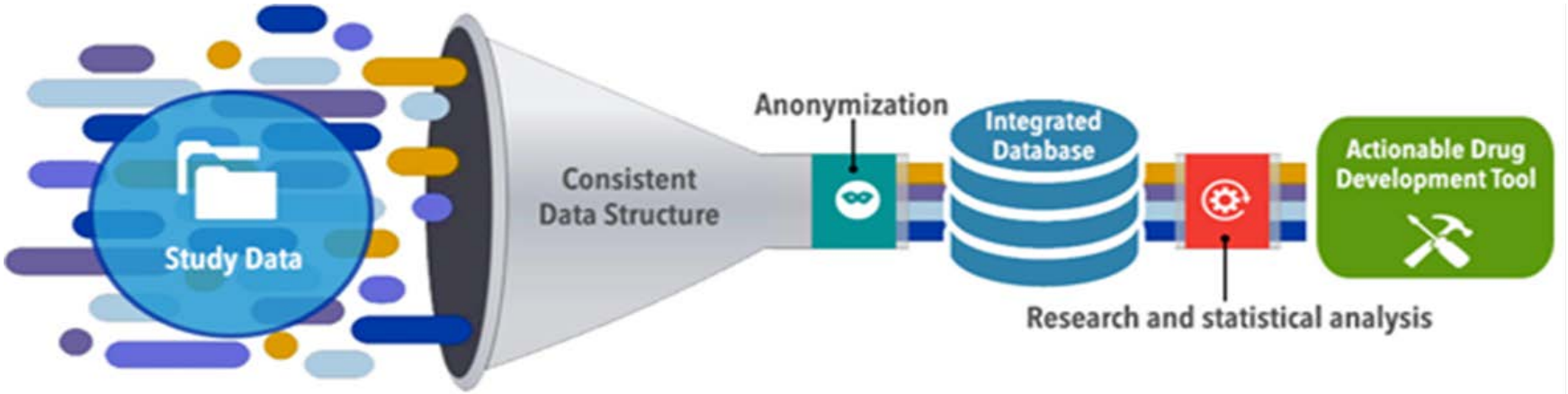
PKD Outcome Consortium — 3/20/12

ID	Task Name	Duration
38	**Map clinical trial data and load database**	**522 days**
54	Map Mayo Data	386 days
55	Map Emory Data	386 days
56	Map U Colorado Data	330 days
58	Upload/VerifyMayo, Emory, Colorado Data	10 days
62	**Data Loaded/Verified In the Database**	**0 days**
64	**Disease Modeling and Simulation**	**528 days**
71	Initiate Modeling and Analysis Phase	0 days
72	Aim 1: Modeling and Simulations Plan	5 days
73	Aim 2: Briefing Package Review	5 days
74	Aim 3: Disease Progression Model	29 days
75	Aim 4: TKV Expansion and Clinical Outcomes	34 days
76	Aim 5: Biomarker Qualification Package	40 days
77	Disease Modeling Results and Review	10 days
78	**Disease Modeling Complete**	**0 days**
80	**Regulatory Qualification Process**	**604 days**
90	BQRT Briefing Book Recommendations	21 days
91	Update BQS Briefing Package	104 days
92	Submit Updated BQS Briefing Package to FDA	0 days
93	Conduct initial BQRT review of Briefing Pkg	5 days
94	Consultation and Advice Phase activities	100 days
95	FDA agreement to proceed to Review Phase	0 days
96	Prepare Final Qualification Package	40 days
97	Internal Review of Final Qualification Package	10 days
98	Finalize Qualification Package	10 days
99	RegulatorySubmission Complete	0 days



Proposal Scope and Timeline

- Development of a data sharing platform for clinical data
- Complete/Update CDISC therapeutic area standard where gaps exist
- Use data to inform the development of regulatory documents and publications



Write & Submit Letter of Intent

Regulatory Input

Write & Submit Qualification Plan

Regulatory Feedback

Execute Plan, Write Results & Submit

Regulatory Review

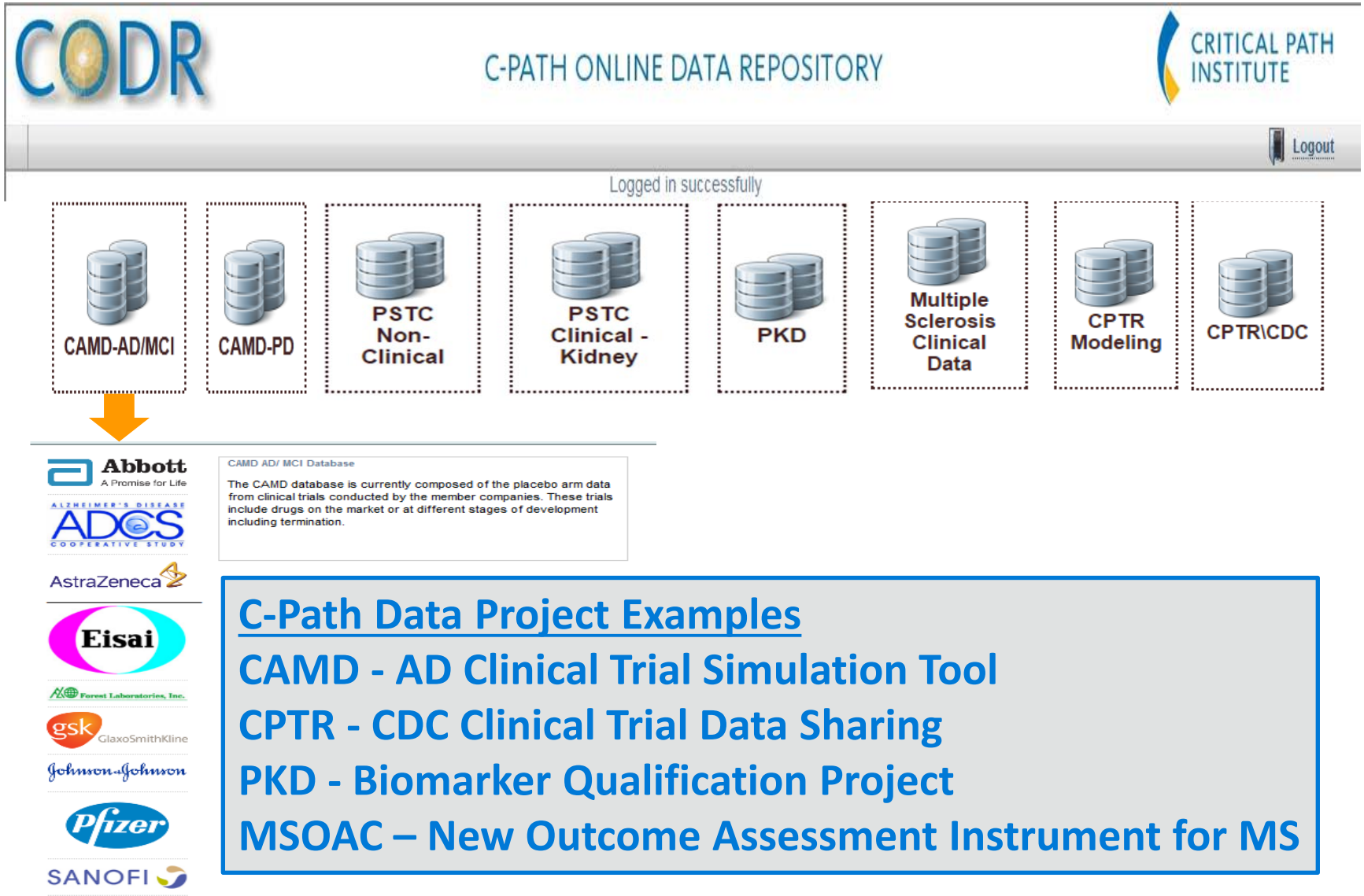
Year 1 **Year 2** **Year 3**

C-Path Policies for Handling of Clinical Data

Key guiding principles:

- We operate as a responsible steward for the clinical data contributed to, used by C-Path, and shared by C-Path
- Data are shared as allowed by contributor
- We will abide by all applicable regulations that govern the use of clinical data

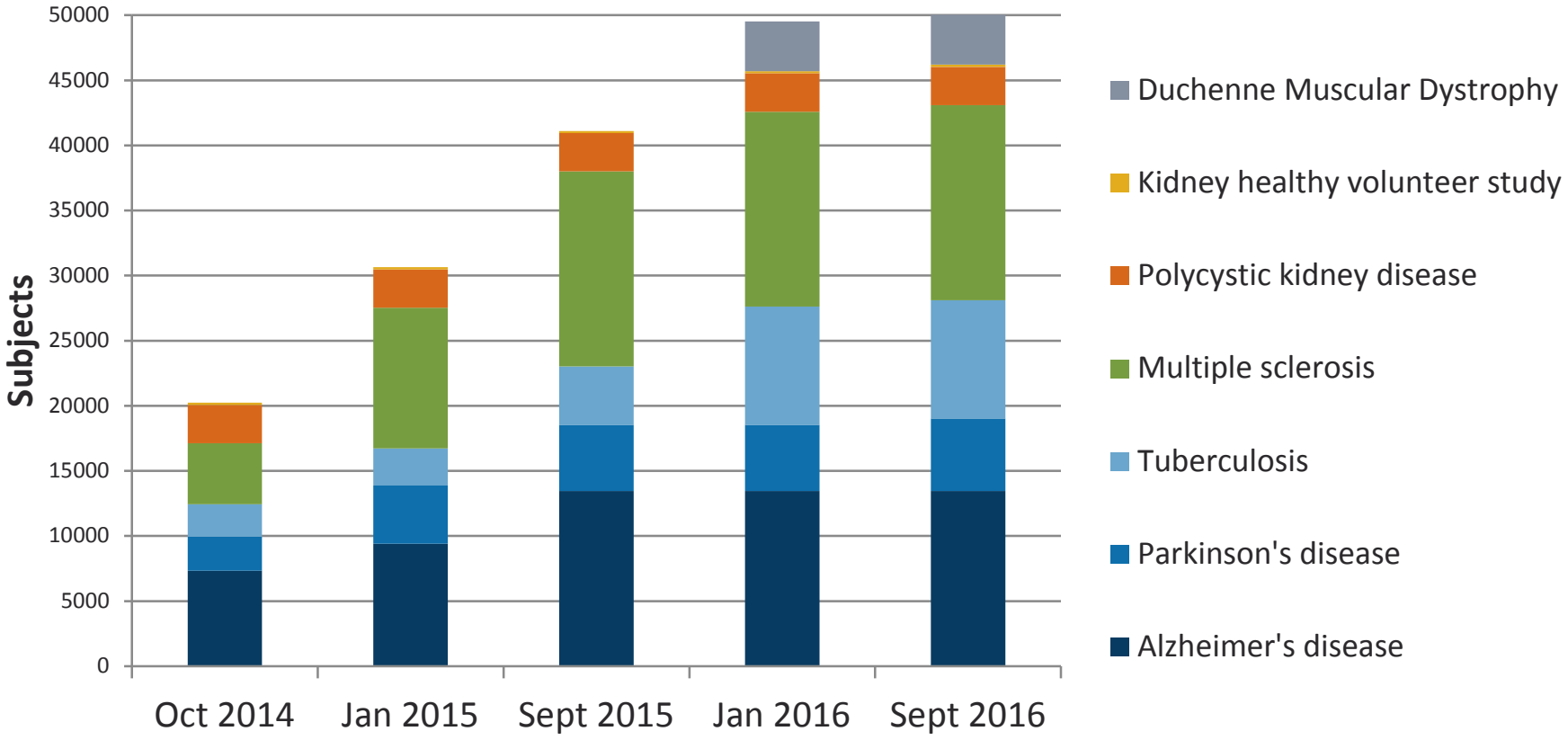
C-Path Online Data Repository



C-Path Data Project Examples

- CAMD - AD Clinical Trial Simulation Tool
- CPTR - CDC Clinical Trial Data Sharing
- PKD - Biomarker Qualification Project
- MSOAC – New Outcome Assessment Instrument for MS

Clinical Data Contributed to C-Path



Clinical Data: 86 Studies, 50,147 Subjects

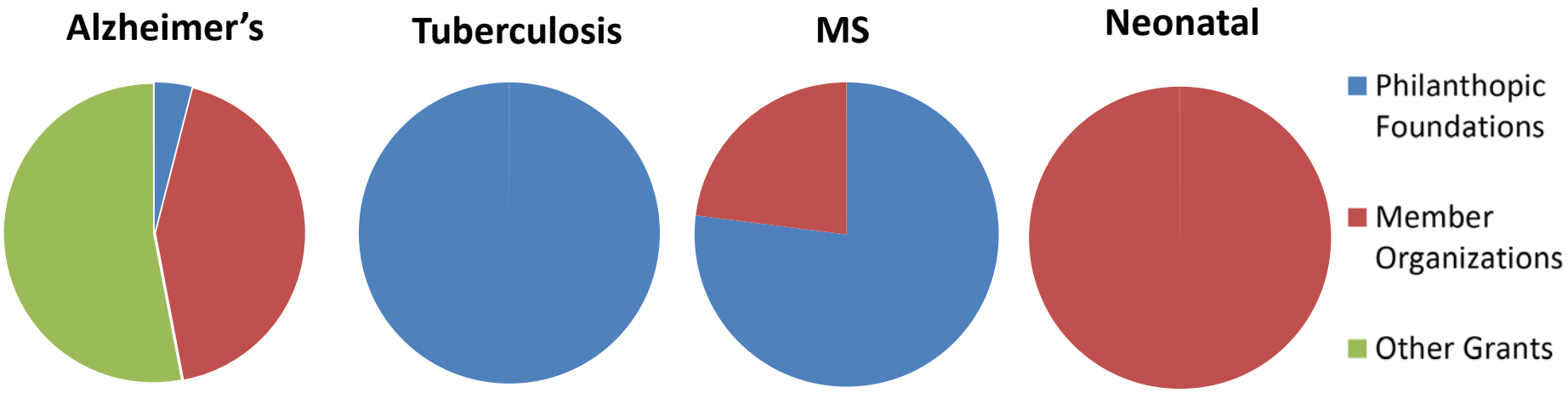
Nonclinical Data: 116 Studies, 6,296 Subjects
ReSeqTB: 3,558 Individual Isolates

Funding Models

Funding potentially provided through multiple sources:

- Philanthropic foundations
- Member organizations
- Other grants
- Combination of one or more of the above

C-Path funding model examples:



Next Steps

- Determine who will participate
- Finalize and sign consortium membership agreements
- Announce and formally launch
- Select leadership and staff working groups
- Begin work –
  - Write regulatory Letter of Intent
  - Locate applicable datasets

Thank you

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FDA

FLINN FOUNDATION

SCIENCE foundation ARIZONA
Innovation at Work

Investigator Perspective

Dr. Åke Lernmark, Lund University

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November 7, 2016

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Investigator Perspective

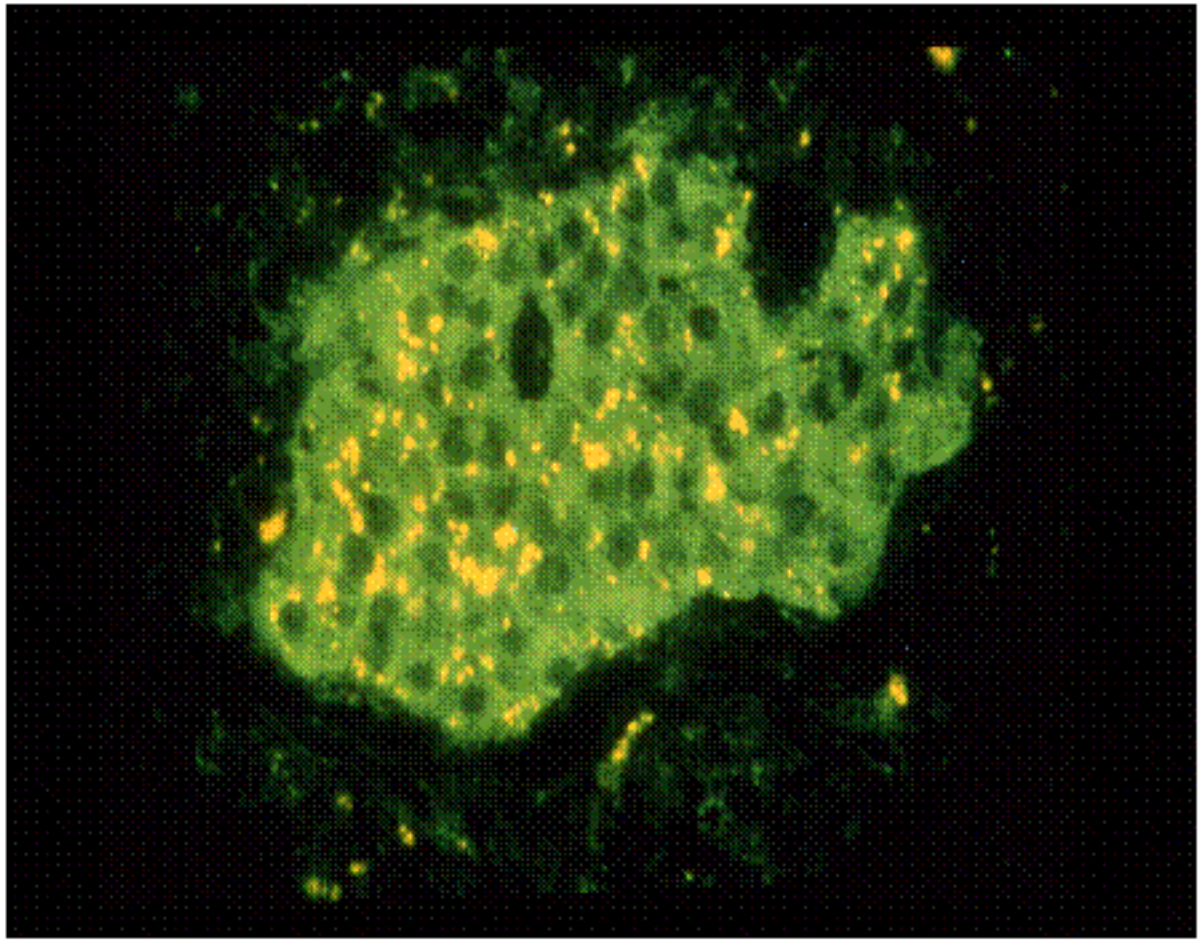
Åke Lernmark
Lund University/CRC
Skåne University Hospital
Malmö Sweden

LUND UNIVERSITY

Type 1 diabetes – an organ-specific autoimmune disease

- Etiology - Genetic – HLA DR-DQ-DP
  - Environmental factors
  - Contributing genetic factors
- Pathogenesis
  - Prodrome at variable rate
  - Autoantibodies are biomarkers
- Clinical onset and diagnosis
  - Replacement therapy - insulin

On the Path to Biomarker Qualification



Cytoplasmic ICA kindly provided by the discoverer Franco Bottazzo

“The long and winding road-1”

- ICA: Indirect Immunofluorescence Assay of frozen sections of human pancreas.
  - Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* 30:1279-83,1974 - NOV
  - MacCuish AC, Irvine WJ, Barnes EW, Duncan LJ. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. *Lancet* 28:1529-31, 1974- DEC
- 1975 – 1982: several indications that ICA in one lab was not the same as in another.

“The long and winding road-2”

- JDRF sponsored the first workshop in Monte Carlo, October 31, 1985
- Gleichmann H, Bottazzo GF. Progress toward standardization of cytoplasmic islet cell-antibody assay. *Diabetes* 36:578-84, 1987.
  - Cytoplasmic islet cell autoantibodies (ICAs) of 13 coded sera were determined by 26 laboratories.
  - The data indicated the requirement of both method improvement and exchange of reference reagents for interlaboratory comparison.
- Immunology of Diabetes Workshops (IDW) was born.

“The long and winding road-3”

- 2nd workshop (1987, Perth, Australia):
- Bonifacio E, Lernmark A, Dawkins RL. Serum exchange and use of dilutions have improved precision of measurement of islet cell antibodies. *J Immunol Methods* 106:83-8, 1988.
  - Coded sera were distributed to 38 laboratories.
  - By including dilutions of sera it was possible to draw a standard curve for each laboratory and this revealed major variations in shape, slope and intercept.
  - A substantial improvement was obtained using each laboratory's standard curve and converting results to units.
- The approach described improves standardisation and will permit laboratories to identify poor assay performance.

- The JDRF Units were born to express levels in relation to a common standard.

“The long and winding road-4”

- Insulin AutoAntibodies (IAA):
- Palmer JP, Asplin CM, Clemons P, Lyen K, Tatpati O, Raghu PK, Paquette TL. Insulin antibodies in insulin-dependent diabetics before insulin treatment. *Science.*222:1337-9, 1983.
- Serum exchange workshops showed that the radiobinding assay was reliable:
  - Greenbaum CJ, Wilkin TJ, Palmer JP. Fifth International Serum Exchange Workshop for Insulin Autoantibody (IAA) Standardization. The Immunology and Diabetes Workshops and participating laboratories. Diabetologia. 35798-800, 1992.

- All **ELISA tests were disqualified.**

- The idea of a conformational epitope was born.

- **IAA is yet to be standardized!!!**

“The long and winding road-5”- cloned autoantigens enter the scene.

- It started with an immunoprecipitate in 1982: **the 64K protein:**
  - GAD65 – cloned in 1991
  - IA-2 - cloned in 1994
  - ZnT8 – cloned in 2007
- **In vitro transcription translation 1992**
  - Several workshops – IDW killed – Immunology of Diabetes Society (IDS) born in 1995 to organize:
  - **Diabetes Autoantibody Standardization Program (DASP)** sponsored by JDRF and CDC.

“The long and less winding road-6”.

- **Workshops:** Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, Eisenbarth GS. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. *Diabetes.* 47:1857-66, 1998.
  - Companies encouraged – ELISAs fell by the wayside
- **WHO standard:** the standard serum used for ICA JDRF Units was used for GADA and IA-2A.

“The WHO standard”.

- Lernmark A, Kolb H, Mire-Sluis T. Towards a World Health Organization (WHO) approved standard sample for islet cell antibodies, GAD65 and IA-2 autoantibodies. *Diabetologia.* 1999 Mar;42(3):381-2, 1999.
- Mire-Sluis AR, Gaines Das R, Lernmark A. The World Health Organization International Collaborative Study for islet cell antibodies. *Diabetologia.* 43:1282-92, 2000.
- WHO Expert Committee on Biological Standards: preparation 97/550 is still available at the National Institute of Biological Standards and Control (NIBSC) as the reference standard for GADA and IA-2A as well as ICA.

- **Islet Autoantibody Standardization Program (IASP) is on-going.**

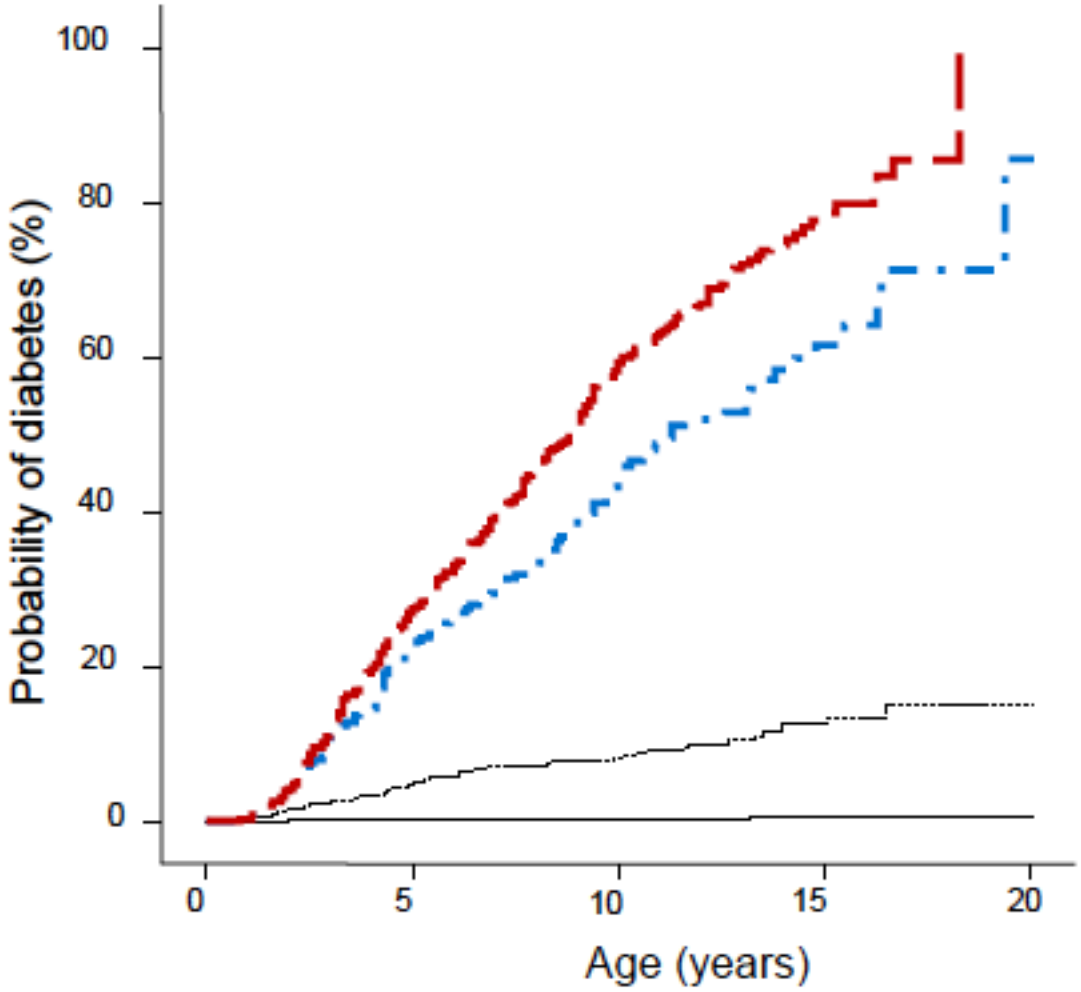
“The DK standard”.

Harmonization of Glutamic Acid Decarboxylase and Islet Antigen-2 Autoantibody Assays for National Institute of Diabetes and Digestive and Kidney Diseases Consortia

Ezio Bonifacio, Liping Yu, Alastair K. Williams, George S. Eisenbarth, Polly J. Bingley, Santica M. Marcovina, Kerstin Adler, Anette G. Ziegler, Patricia W. Mueller, Desmond A. Schatz, Jeffrey P. Krischer, Michael W. Steffes, and Beena Akolkar

J Clin Endocrinol Metab, July 2010, 95(7):3360–3367

CHILDREN WITH TWO OR MORE ISLET AUTOANTIBODIES WILL DEVELOP DIABETES.



JAMA. 2013;309(23):2473-2479.

defini
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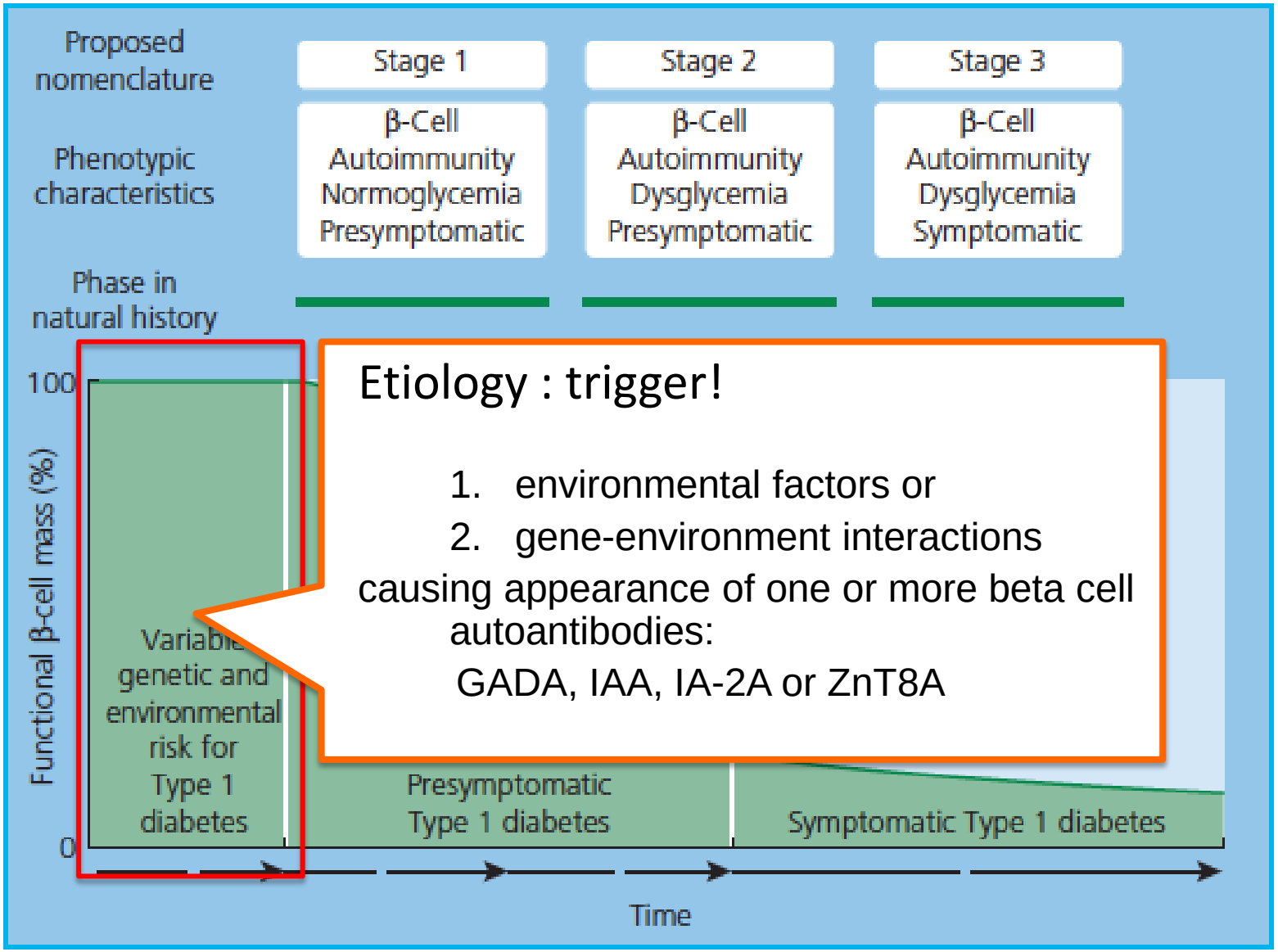
type 1 d

Staging autoimmune (type 1) diabetes



INVESTIGATOR PERSPECTIVE

- **Screening for primary prevention**
  - Subjects at increased genetic risk
    - Induce immune tolerance to (pro)insulin (PrePoint) – HLA selected – DR4-DQ8
    - Induce immune tolerance to GAD65 – DR3-DQ2
- **Screening for secondary prevention**
  - Subjects with autoantibodies and genetic risk
    - Oral insulin (on-going TrialNet)
    - Induce immune tolerance (IA-2, insulin, GAD65 and ZnT8)
    - Other immunomodulatory and combination therapies

What would be the HLA-DQ genotype to select?

The case for Sweden:

DQ genotype	Patients %	Controls %	OR
2/8	28	3.5	10.6
8/8	11	1.7	7.1
8/6.4	5	1.2	4.3
8/5.1	9.3	2.7	3.7
8/4	4 .6	1.4	3.5
2/2	5.1	1.7	3.1
2/9	1.0	0.5	2.2
8/6.3	3.3	2.0	1.7
2/6.4	2.2	1.3	1.7
	69.0	**16.0**	

From the Swedish Better Diabetes Diagnosis (BDD) study:

Patients: n= 4000
Controls: n= 2000

Persson, Carlsson et al.
Submitted for publication

Typing by linked SNPs

Background: More than 50 regions of the human genome confer T1D susceptibility.

Aim: identify sets of SNP combinations to predict T1D in 4,574 patients and 1,207 controls.

Results: AUC 0.87 in the T1DGC set
AUC 0.84 in the validation set.
HLA plus nine SNPs from the PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3 and RNLS genes better than HLA alone.

Winkler C, Krumsiek J, Buettner F, Angermüller C, Giannopoulou EZ, Theis FJ, Ziegler AG, Bonifacio E. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. Diabetologia. 2014 Dec;57(12):2521-9.

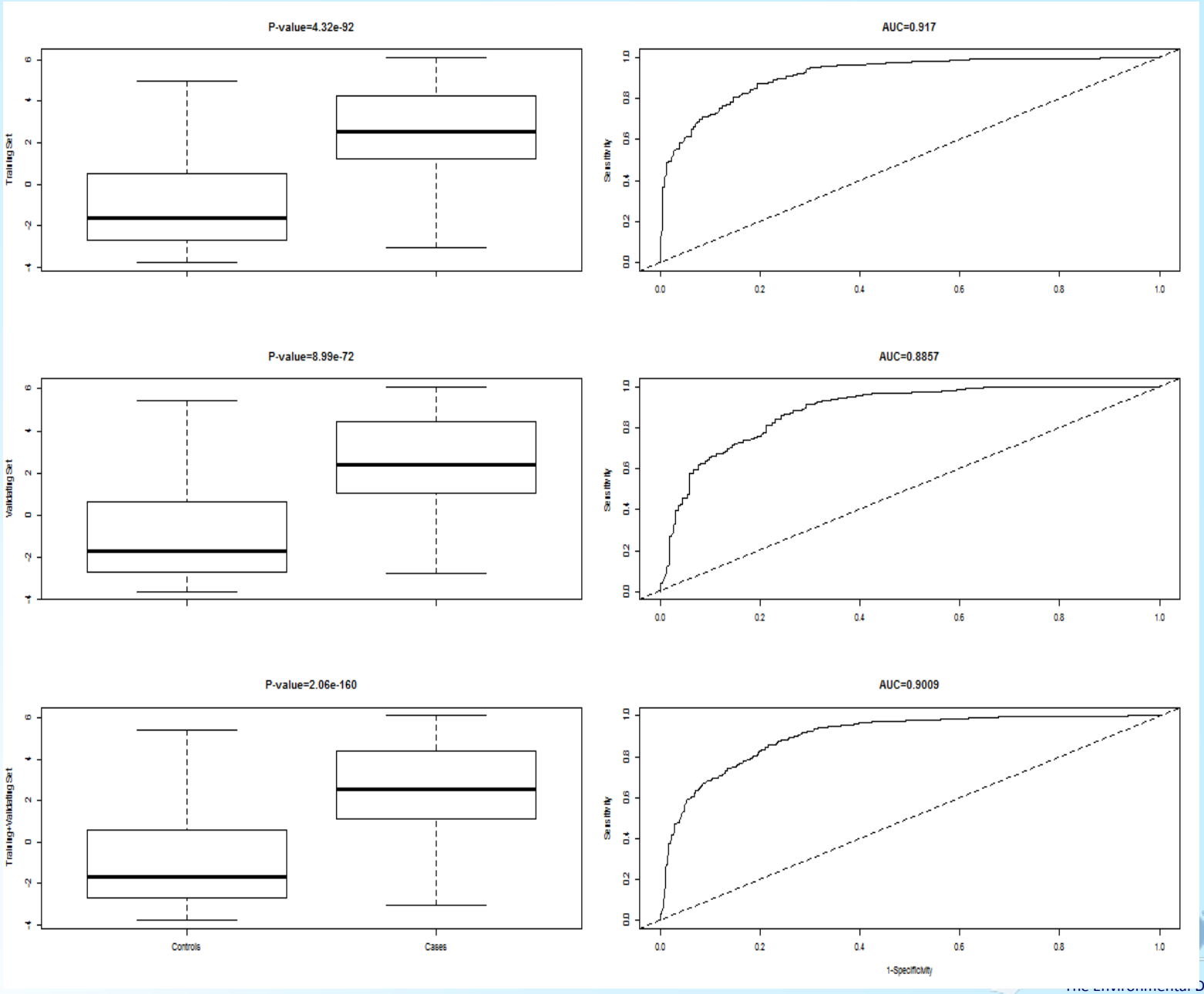
Next Generation Sequencing

Lue Ping Zhao,[1] Shehab Alshiekh,[2] Michael Zhao,[1] Annelie Carlsson,[3] Helena Elding Larsson,[2] Gun Forsander,[4] Sten A. Ivarsson,[2] Johnny Ludvigsson,[5] Ingrid Kockum,[6] Claude Marcus,[7] Martina Persson,[7] Ulf Samuelsson,[5] Eva Örtqvist,[8] Chul-Woo Pyo,[9] Wyatt C. Nelson,[9] Daniel E. Geraghty,[9] and Åke Lernmark,[2] for the Better Diabetes Diagnosis (BDD) Study Group*

Next-Generation Sequencing Reveals That *HLA-DRB3*, *-DRB4*, and *-DRB5* May Be Associated With Islet Autoantibodies and Risk for Childhood Type 1 Diabetes

Diabetes 2016;65:710–718 | DOI: 10.2337/db15-1115

Zhao LP, Bolouri H, Zhao M, Geraghty DE, Lernmark Å; Better Diabetes Diagnosis Study Group.. An Object-Oriented Regression for Building Disease Predictive Models with Multiallelic HLA Genes. Genet Epidemiol. 2016 May;40(4):315-32.



Boxplots of risk scores by controls and cases (left panels) and associated ROC curves (right panels) for subjects in the training set only, validating set only and both training and validating sets.

Conclusion, so far……

- **HLA typing at birth (cord blood or PKU) to select 15-20% of newborns may identify almost 80% of subjects at life time risk for T1D.**
- **Primary prevention end-points:**

IAA –First: HLA DR4-DQ8
1-3 years of age – declining thereafter

GADA- First: HLA DR3-DQ2
3 years and older

Does preventing a child from IAA or GADA also prevent later T1D?

NEWBORNS

- **HLA RISK**
- **PRIMARY PREVENTION**
- **QUALIFIED AUTOANTIBODIES AS END-POINT**
  - **ORAL INSULIN – (Pre-POINT is the model)**

CHILDREN (2-18 years)

- AUTOANTIBODIES – batched type of screening; capillary samples, DBS
- PREVENT THE APPEARANCE OF 2nd, 3rd OR 4th ISLET AUTOANTIBODY
- PREVENT CLINICAL ONSET OF DIABETES

- *Raab J, Haupt F, Scholz M, Matzke C, Warncke K, Lange K, Assfalg R, Weininger K, Wittich S, Löbner S, Beyerlein A, Nennstiel-Ratzel U, Lang M, Laub O, Dunstheimer D, Bonifacio E, Achenbach P, Winkler C, Ziegler AG; Fr1da Study Group.. Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study. BMJ Open. 2016 May 18;6(5):e011144*.

TREATMENT IN CURRENT RESEARCH EFFORTS.

- PRIMARY PREVENTION
  - Oral insulin (Pre-Point)
  - Oral GAD65 (Planned)
  - Combination therapy – induce tolerance
- SECONDARY PREVENTION
  - Oral insulin (TrialNet TN-07 in 2017)
  - Alum-GAD (Helena Elding Larsson in 2017)

WHAT'S IN IT FOR INVESTIGATORS?

- QUALIFIED BIOMARKERS
  - Enable work with primary health care
  - Enable work with hospital laboratories – especially if methods without radioactivity are used
- QUALIFICATION & ACCREDITION
  - Spark interest from industry to develop and improve assays for autoantibodies
  - Expand autoantibody testing in adult diabetes
  - Begin autoantibody testing of schoolchildren

THANK YOU!

Open Discussion

Q & A

Summary & Next Steps

Steve Broadbent, COO

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Next Steps

- Determine who will participate
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