III. ADMINISTRATIVE STRUCTURE

A. HISTORY OF THE TYPE 1 DIABETES GENETICS CONSORTIUM

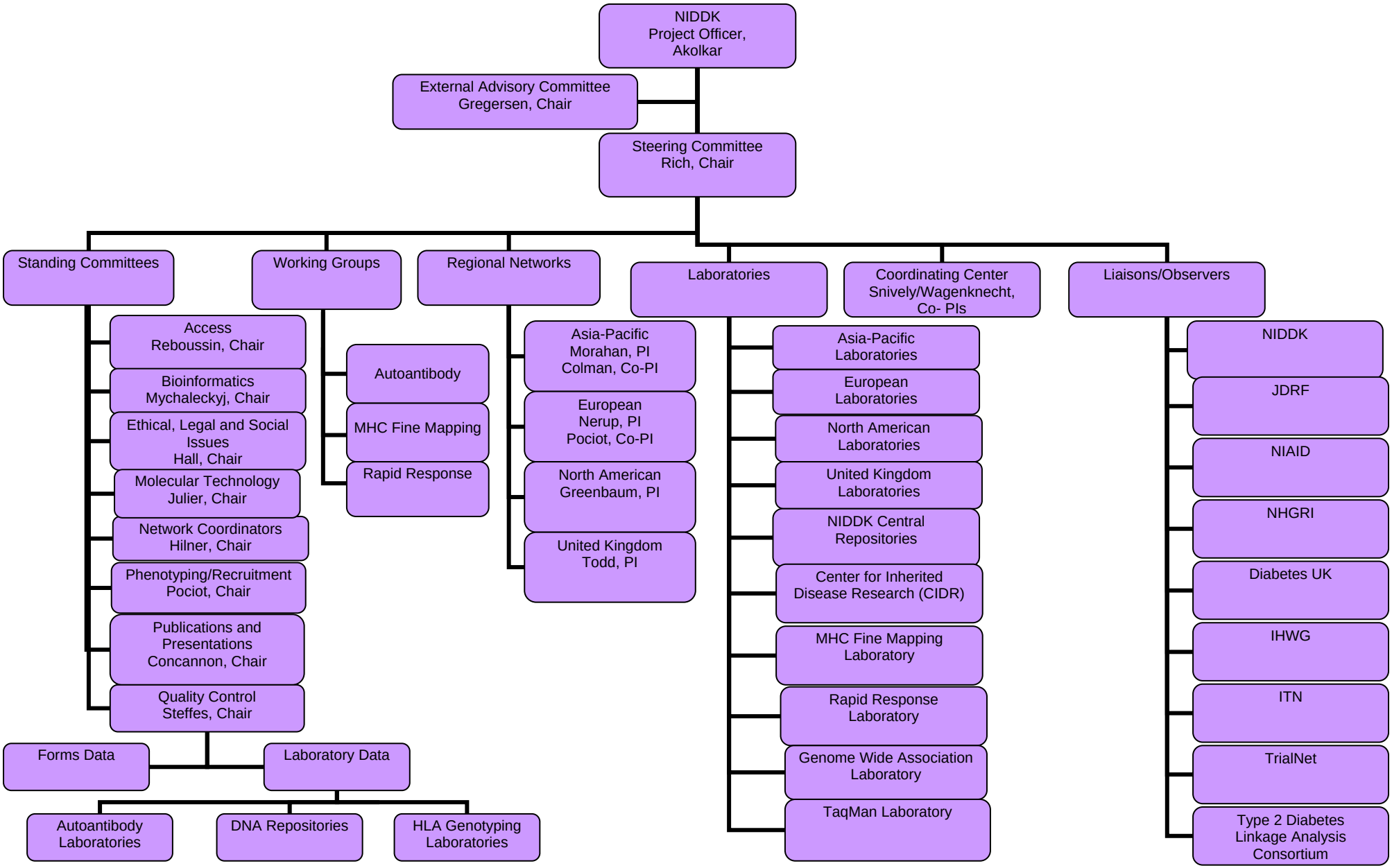
The formation of the Type 1 Diabetes Genetics Consortium (T1DGC) dates back to a meeting at National Institutes of Health (NIH) in November 1998 and its construction began with a meeting in Skagen, Denmark in April 2000. The "Diabetes Genetics Y2K Workshop" was hosted by Drs. Jørn Nerup and Flemming Pociot, and provided a venue for a small group of scientists to discuss the needs of the field to detect genes that determine risk for type 1 diabetes. Participants in the meeting included Drs. Pat Concannon, Nancy Cox, Cecile Julier, Stephen Rich and John Todd. After discussing the current status of the field and approaches to identifying complex disease susceptibility genes, a consensus was reached that collaboration and collection of samples from a large number of families were of greatest need.

Following the Skagen workshop, a message was sent by Dr. Stephen Rich to Dr. Robert Goldstein (Chief Scientific Officer, JDRF) on May 24, 2000, suggesting that the Juvenile Diabetes Research Foundation (JDRF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) could facilitate the development of a collaboration to find type 1 diabetes susceptibility genes. In this message, it was suggested that a focused collaborative effort was needed to: 1) merge the existing genome screen data sets into a single unit to allow a more focused evaluation of regions of genetic interest; 2) to begin to identify laboratories capable of collaborating on specific regions of the genome to begin collaborative positional cloning; and 3) to consider collecting additional families to provide sufficient statistical power to detect the genes of effect smaller than human leukocyte antigen (HLA) but of the magnitude of *INS/IDDM2* (odds ratio = 2.5-3 and calculated $\lambda_s = 1.12$). In response to this request, Dr. Allen Spiegel (Director, NIDDK) and Dr. Goldstein (Chief Scientific Officer, JDRF) established a meeting on "Genetics of Type 1 Diabetes" which was held in Bethesda, MD, November 20, 2000. The purpose of the meeting was to assess the progress toward finding genes for type 1 diabetes and to discuss strategies and resources needed to accelerate the process. The meeting was chaired by Dr. Stephen Rich and included over 50 scientists and NIH/foundation program staff. Scientists speaking at the meeting included Drs. Pat Concannon, Nancy Cox, Cecile Julier, Grant Morahan and John Todd. There was a free exchange of ideas concerning issues and limitations that restrict success in finding type 1 diabetes genes. The clear message from the meeting was that a "consortium" was needed to establish resources, provide support for management and coordination of the resources, and stimulate collaboration among scientists. As a result of the Bethesda meeting, the T1DGC was established.

B. STRUCTURE OF THE TYPE 1 DIABETES GENETICS CONSORTIUM

The T1DGC is comprised of the NIDDK Project Office, an External Advisory Committee (EAC), the Steering Committee, Regional Networks, Standing Committees, Regional Laboratories, a Coordinating Center and programmatic liaisons and observers. Figure 1 presents the overall study organization. Membership in the T1DGC is open to all investigators with research focused on the genetic basis of type 1 diabetes mellitus. The Consortium Agreement (**Chapter IV**, *Study Policies*) outlines the ways in which individuals can participate in T1DGC activities as well as describing the responsibilities of and benefits to investigators.

Figure 1. Type 1 Diabetes Genetics Consortium Study Organization



The source of support for the T1DGC came from several mechanisms, jointly sponsored by the NIDDK and the JDRF. An initial research grant was awarded to Dr. Stephen Rich to combine the genome scan data from the North American, United Kingdom and European networks (individually published) and provide the preliminary data for an NIH application. Support for meetings of the Steering Committee to plan the NIH application came from JDRF (travel and support for non-U.S. meetings) and the NIDDK (travel and support for U.S. meetings). Administrative supplements from the NIDDK to Dr. Stephen Rich were made to support administrative planning, the establishment of the T1DGC web site (to further communications among members), and the initiation of a Coordinating Center (see section 3, below, for detail). The implementation of the T1DGC plans into an NIH application was led by Dr. Stephen Rich (who serves as Principal Investigator). The application was submitted in November 2001 and funding for the T1DGC was received September 15, 2002.

1. Steering Committee

The NIDDK and JDRF sponsored a meeting of international investigators centered on the needs of the scientific community to further research in type 1 diabetes genetics. The meeting was held in November 2000, with an agreement to establish a resource of family materials and supporting mechanisms to enhance positional cloning of type 1 diabetes susceptibility and resistance genes. The NIDDK extended invitations to establish the T1DGC Steering Committee. Members of the Steering Committee agreed to guide the development of the project, participating in face-to-face meetings and conference calls as required to accomplish the study's goals. The responsibility of the Steering Committee included the construction of an NIH grant application to obtain funding to support the goals of the Consortium. The Steering Committee members include:

Member	Institution	Location	Country
Beena Akolkar	NIDDK	Bethesda, MD	USA
Pat Concannon	University of Virginia	Charlottesville, VA	USA
Henry Erlich	Roche Molecular Systems	Pleasanton, CA	USA
Cecile Julier	Inserm UMR, Faculté de Médecine Denis-Diderot	Paris	France
Grant Morahan	Western Australia Institute for Medical Research	Perth	Australia
Jørn Nerup	Hagedorn Research Institute	Gentofte	Denmark
Flemming Pociot	Hagedorn Research Institute	Gentofte	Denmark
Stephen Rich (Chair)	University of Virginia	Charlottesville, VA	USA
John Todd	Cambridge University	Cambridge	UK

2. Programmatic Observers and Liaisons

In view of the encompassing nature of the Consortium and the implications of establishing resources needed to positionally clone genes, two additional components were added to the structure of the Steering Committee. First, programmatic representatives were appointed to represent key agencies as observers and, second, liaisons to existing initiatives in type 1 and 2 diabetes research were appointed.

3. Regional Networks

The Regional Networks are responsible for the recruitment of affected sib pair (ASP) families, trio families, cases and controls. The T1DGC is divided into four networks (Asia-Pacific, European, North American, and United Kingdom). Specific information regarding each of the networks, including recruitment goals, is provided.

a. Asia-Pacific Network:

Regional Network Center:	Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia
Co-Principal Investigators:	Grant Morahan, PhD, and Peter Colman, MD
Recruitment goal:	340 ASP families; trios, cases and controls in low prevalence populations
Participating countries:	Australia, India, Malaysia, New Zealand, Philippines, Singapore, Thailand

Number of data collection sites: 20

b. European Network:

Regional Network Center:	Hagedorn Research Institute in Gentofte, Denmark
Co-Principal Investigators:	Jørn Nerup, MD and Flemming Pociot, MD, DMSc
Recruitment goal:	1,200 ASP families; trios, cases and controls in low prevalence populations
Participating countries:	Austria, Belgium, Cameroon, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Slovenia, Spain, Sweden, Switzerland, Turkey

Number of data collection sites: 83

c. North American Network:

Network Regional Center:	Benaroya Research Institute in Seattle, WA, USA
Principal Investigator:	Carla Greenbaum, MD
Recruitment goal:	1,100 ASP families; trios, cases and controls in low prevalence populations
Participating sites:	TrialNet sites in Florida, Texas, San Francisco, Los Angeles, Stanford, Miami, Minnesota, Seattle, Toronto, Pittsburgh, Indiana, and New York City; SEARCH sites in South Carolina, Ohio, California, and Washington; and designated collection centers in Augusta, Baltimore, Billings, Boise, Boston, Bronx, Buffalo, Chicago, Columbus, Denver, Edmonton, Grand Rapids, Greenville, Houston, Iowa City, Little Rock, Milwaukee, Montreal, Morristown, Nashville, New Hyde Park, Oakland, Ogden, Omaha, Orange, Philadelphia, Richmond, Rochester, Salt Lake City, San Antonio, Seattle, Spokane, St. Petersburg, Syracuse, Vancouver, Winnipeg, Worcester, and Wynwood

Number of data collection sites: 57

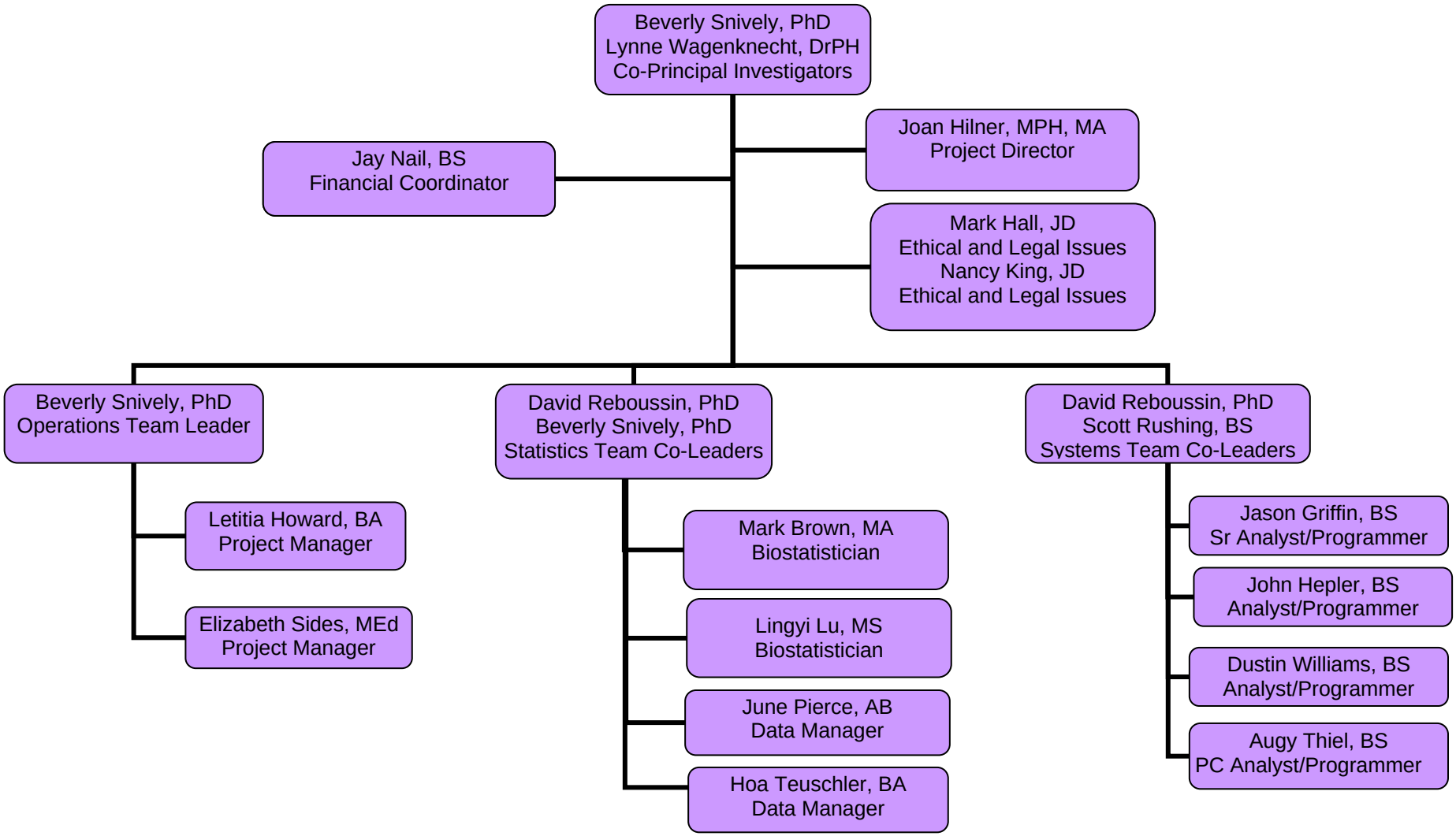
d. United Kingdom Network:
Network Regional Center: Cambridge University in Cambridge, UK
Principal Investigator: John Todd, PhD
Recruitment goal: 160 ASP families
Participating sites: Hospitals and clinics that participated in UK GRID project
Number of data collection sites: 48

4. Coordinating Center

In order to provide the appropriate infrastructure for the logistical aspects of the study, a Coordinating Center was established at Wake Forest University Health Sciences in Winston-Salem, NC, USA. The Coordinating Center facilitates the day-to-day operations of the T1DGC in three general areas: (1) operations; (2) statistics; and (3) systems. Personnel at the Coordinating Center include faculty with expertise in project management, statistical genetics, genetic epidemiology, epidemiology, biostatistics, clinical trials, ethical and legal issues, bioinformatics, and laboratory procedures.

The Coordinating Center is responsible for the fiscal aspects of the study; maintaining the T1DGC web site; preparation of reports, meeting agendas and materials; tracking overall recruitment progress; development of manuals of operations and procedures, and data analysis plans. Figure 2 illustrates the overall organization of the Coordinating Center.

Figure 2. Type 1 Diabetes Genetics Consortium Coordinating Center Organization



5. Standing Committees

The T1DGC has established eight standing Committees to perform the work required to meet the study's goals. It is the intent that membership in each committee includes individuals from each of the networks. The charge and the Chair for each committee are provided. Membership of each committee can be found on the T1DGC web site.

a. Access Committee
Chair: David Reboussin, PhD

The Access Committee will be responsible for recommending policy for consideration and approval by the T1DGC Steering Committee and developing procedures for implementation in the following areas:

- Access to stored genetic samples maintained by the T1DGC
- Access to stored serum and plasma specimens maintained by the T1DGC
- Access to T1DCG study databases
- Access to reports and other study materials stored on the T1DGC web site

In doing so, the Access Committee will:

- Consider issues of security and confidentiality in protecting study participants
- Monitor and regularly inform the T1DGC Steering Committee on the availability of samples and data through reports provided by the study repositories and the Coordinating Center
- Coordinate a process for reviewing petitions to obtain access to T1DGC study materials and report regularly to the Steering Committee on the petition process

b. Bioinformatics Committee
Chair: Josyf Mychaleckyj, MA, DPhil

The charter of the Bioinformatics Committee is to promote and facilitate the application of bioinformatics techniques to the mapping of type 1 diabetes susceptibility genes by investigators in the Consortium. The Committee will strive to:

- Share information on best practices and emerging techniques for the bioinformatics support of gene mapping projects
- Develop strategies for common computational infrastructure, and if necessary, specify new components that should be purchased or developed
- Identify computational tools and services that can usefully be deployed at the Consortium level, to support and assist multiple groups or networks
- Specify repositories and interfaces to integrate and distribute the large amount of existing, and novel, phenotypic and genotypic data that will be generated within the Consortium
- Identify standards and formats for data exchange between research groups and networks
- Identify mechanisms to assist research groups of all types in fully utilizing public genome resources, and available informatics resources of the Consortium

c. Ethical, Legal and Social Issues (ELSI) Committee
Chair: Mark Hall, JD

The ELSI Committee will be responsible for promoting the ethical and legal conduct of this research study. In doing so, the Committee will:

- Draft model informed consent form templates for approval by the Steering Committee
- Recommend policies for minimum requirements to meet ethical standards
- Advise Regional Networks on adapting informed consent forms to local requirements
- Advise the Steering Committee regarding intellectual property issues
- Address other general legal and ethical issues that arise and are within the competence of committee members to consider

d. Molecular Technology Committee
Chair: Cecile Julier, PhD

The Molecular Technology Committee will be responsible for recommending and advising the Steering Committee regarding issues related to advances in this area. In doing so, the Committee will:

- Evaluate the cutting-edge technology that could be used by Consortium investigators
- Recommend policy regarding genotyping and sequencing for review and approval by the Steering Committee

e. Network Coordinators Committee
Chair: Joan Hilner, MPH, MA

The Network Coordinators Committee will:

- Review, discuss and resolve issues surrounding network and clinic recruitment, study protocol, and overall operations
- Serve as a study resource of network-specific information and ideas
- Monitor quality of data collection and provide feedback to network clinics

f. Phenotyping/Recruitment Committee
Chair: Flemming Pociot, MD, DMSc

The Phenotyping/Recruitment Committee will:

- Develop recommendations for data and specimens to be collected from participants, including the definition of type 1 diabetes as well as and the laboratory, physical, and demographic measures
- Assist the Coordinating Center in the development of study forms and manuals that relate to the study phenotypes
- Monitor study recruitment and provide guidance to the Regional Networks in the recruitment of families

- Serve as an *ad hoc* Eligibility Committee and review / adjudicate the eligibility of cases submitted to the Committee by the Regional Networks

g. Publications and Presentations Committee
Chair: Pat Concannon, PhD

The Publications Committee will be responsible for recommending policy for consideration and approval by the Steering Committee and develop procedures for implementing approved policies to:

- Assure and expedite orderly and timely presentations and publications
- Assure that all investigators have the opportunity to participate and be recognized in the study-wide presentation of T1DGC papers
- Review proposed T1DGC Study publications and presentations in a timely manner
- Assure that press releases, interviews, presentations, and publications of T1DGC Study materials are accurate, objective, and do not compromise the scientific integrity of this collaborative study
- Assure that the T1DGC is suitably acknowledged in all publications arising from use of T1DGC resources through developing and recommending guidelines for such acknowledgement (*e.g.,* ranging from authorship to mention in acknowledgements section)
- Assist the Coordinating Center in developing a publications system for tracking progress on each proposed manuscript and maintain a complete up-to-date list of T1DGC Study presentations and publications on the study web site

h. Quality Control Committee
Chair: Michael Steffes, MD, PhD

The Quality Control Committee will be responsible for monitoring the quality of data collection, laboratory measures and genotyping for the T1DGC. There are four Quality Control Committees: Autoantibody and Storage Laboratories, DNA Repositories, HLA Genotyping Laboratories, and Forms Data. Each of these Committees will:

- Plan and design appropriate measures and techniques that promote and assess data quality
- Oversee implementation of the quality control procedures by working with the Coordinating Center, Regional Networks, clinics and laboratories
- Interact with the Coordinating Center to provide timely feedback to clinics and laboratories
- Meet on a periodic basis to review the quality of the data
- Advise the Regional Network Centers and Steering Committee regarding issues of data quality
- Prepare a summary document that periodically reports the quality of the data collected
- Review (and propose as needed) quality control procedures for proposals requesting access to T1DGC samples

6. Working Groups

The T1DGC established three Working Groups to perform the work required to meet the study's goals. It is the intent that membership in each working group includes individuals from each of the networks. The charge of each working group is provided. Membership of each working group is located on the T1DGC web site.

a. Autoantibody Working Group

The T1DGC Autoantibody Working Group (AA WG) is charged with the analysis of the autoantibody data generated under the guidance of the Type 1 Diabetes Genetics Consortium (T1DGC). The ultimate objective of the AA WG is to better define the relationship between autoantibody measures and phenotypic and genotypic characteristics in an attempt to elucidate those relationships that merit further analytic examination. The AA WG is expected to:

- use the autoantibody and specified phenotypic and genotypic data to its fullest extent; and
- include all data from all participants in primary analyses, regardless of contributing T1DGC recruitment network; however, secondary data analyses using network membership or other data (*e.g.*, autoimmune disease status) would be permissible

b. MHC Fine Mapping Working Group

The T1DGC MHC Fine Mapping Working Group is charged with the analysis of the genetic data generated under the guidance of the Type 1 Diabetes Genetics Consortium (T1DGC). The ultimate objective of the MHC WG is to better define the region(s) of the MHC that would likely contain type 1 diabetes susceptibility genes and, hence, would merit further genetic (and analytic) examination. The MHC WG is expected to:

- use the genetic data to its fullest extent, including information from SNPs, microsatellite markers, and classical HLA genotyping; and
- include all data from all participants in primary analyses, regardless of contributing T1DGC recruitment network; however, secondary data analyses using network membership or other data (*e.g.*, age at onset, antibody status, etc.) would be permissible

c. Rapid Response Working Group

A Rapid Response Working Group has been established for each gene being studied in the T1DGC. Each Rapid Response Working Group will be charged with leadership in the analysis and interpretation of the role of the specified type 1 diabetes candidate gene data generated as part of the T1DGC. Specifically, each Rapid Response Working Group will:

- integrate the tagged-SNP data for the candidate gene with the phenotypic data obtained on the family materials,
- perform necessary analyses for quality control and quality assurance
- conduct statistical genetic analyses of the data, including both linkage and family-based association methods
- work with the T1DGC to produce manuscripts and reports to the T1DGC community

Responsibilities of each Rapid Response Working Group Leader include the following:

- solicit people who want to participate, per criteria above;

- report on progress to T1DGC Steering Committee;
- work with T1DGC Coordinating Center to keep RR WG members informed; and
- submit a manuscript outline to the T1DGC Publications and Presentations Committee.

7. Laboratories

Creation of cell lines, autoantibody measures, HLA genotyping, extraction of DNA from cell lines and cell packs, and storage of serum and plasma samples will occur in laboratories established in each of the Regional Networks. In general, each network will have three types of laboratories: (1) a DNA Repository where cell lines will be created and DNA extracted for study-directed genotyping projects, HLA genotyping, and Contributing Investigators; (2) an Autoantibody Laboratory where GAD65 and IA-2_{ic} autoantibodies will be measured in probands, affected siblings and cases and specimens (serum and plasma) will be stored for future use; and (3) a HLA Genotyping Laboratory where class I locus (A, B, C), class II locus (DRB1, DQA1, DQB1, DPA, DPB) and SNPs (*INS-23Hph1* and *CTLA4*) will be typed.

Cell lines, DNA, plasma and serum samples from every T1DGC participant will be forwarded from the Regional Laboratories to the NIDDK Central Repositories in the U.S.

a. Asia-Pacific Network Laboratories:

DNA Repository:	Australian Red Cross Blood Service Melbourne, Australia Brian Tait, PhD
Autoantibody Laboratory:	Royal Melbourne Hospital Victoria, Australia Peter Colman, MD
HLA Genotyping Laboratory:	Royal Melbourne Hospital Victoria, Australia Brian Tait, PhD

b. European Network Laboratories:

DNA Repository:	Ulm University Ulm, Germany Bernhard Boehm, MD
Autoantibody Laboratory:	University of Bristol Bristol, United Kingdom Polly Bingley, MD
HLA Genotyping Laboratory:	Malmö University Hospital Malmö, Sweden Joyce Carlson, MD, PhD

c. North American Network Laboratories:

DNA Repository:	Fred Hutchinson Cancer Research Center Seattle, WA, USA John Hansen, MD
Autoantibody Laboratory:	University of Colorado Health Sciences Center Denver, CO, USA George Eisenbarth, MD, PhD
HLA Genotyping Laboratories:	Children's Hospital and Research Center at Oakland Oakland, CA, USA Janelle Noble, PhD
	Roche Molecular Systems Pleasanton, CA, USA Henry Erlich, PhD

d. United Kingdom Network Laboratories:

DNA Repository:	JDRF/ WT Diabetes and Inflammation Laboratory Cambridge, UK John Todd, PhD
Autoantibody Laboratory:	University of Bristol Bristol, United Kingdom Polly Bingley, MD
HLA Genotyping Laboratory:	Malmö University Hospital Malmö, Sweden Joyce Carlson, MD, PhD

e. NIDDK Central Repositories:

Biosample Repository:	Fisher Bioservices Corporation Rockville, MD, USA Heather Higgins, MS
Genetics Repository:	Rutgers, The State University of New Jersey New Brunswick, NJ, USA Jay Tischfield, PhD
Data Repository:	Research Triangle Institute Research Triangle Park, NC, USA Anthony Cuticchia, PhD

f.	Center for Inherited Disease Research:	Johns Hopkins University Baltimore, MD, USA David Valle, MD
g.	MHC Fine Mapping Laboratory:	Wellcome Trust Sanger Institute Hinxton, UK Panos Deloukas, PhD
h.	Rapid Response Laboratory:	Broad Institute of MIT and Harvard Cambridge, MA, USA Stacey Gabriel, PhD
i.	Genome Wide Association Laboratory:	Illumnia, Inc. San Diego, CA, USA Jay Flatley, MS
j.	TaqMan Laboratory:	JDRF/WT Diabetes and Inflammation Laboratory Cambridge, UK John Todd, PhD