# ISPAD 2012

# INVITED SPEAKER

## Presidents Welcome | Opening Lecture

INV01

### Global Challenges for Integrated Pediatric Diabetes Care: Do we Need to Redefine the Health System for Diabetes?

D. Beran
*University of Geneva, Geneva, Switzerland*

Ninty years after the first person received insulin, care for Type 1 diabetes has been revolutionised in the developed world with dramatic increases in life-expectancy. These developments within the health system have been linked to healthcare worker training, education, organised centres for care, diagnostic tools and other elements. However, in resource poor settings these developments in diabetes care have not had the same impact as life-expectancy is still as low as 1 year. Much of this is due to lack of access to insulin, trained healthcare workers and general lack of awareness about the management of Type 1 diabetes.

In parallel we have seen an increase in obesity and Type 2 diabetes in children and adolescents. The causes of Type 2 diabetes are diverse and are closely linked to changes in society. Management of obesity and Type 2 diabetes in children and adolescents is difficult and as of yet most interventions have shown little long-term success.

Many definitions of integrated care exist, but the World Health Organization defines it as ''the organization and management of health services so that people get the care they need, when they need it, in ways that are user-friendly, achieve the desired results and provide value for money.''

Integrated care to date has focused solely on the medical perspective. For Type 1 diabetes in developed countries have we reached the limits of this medical perspective? In developing countries due to the lack of resources within the health system means that additional focus should be on the family and community. Obesity and Type 2 diabetes are intimately linked with the environment and what the health system can do to have an impact is limited. There is the need to redefine the health system and the concept of integrated care. There should be a focus on the individual's needs and these should be integrated within the environment(s) that people live in to ensure that we manage the person as an individual and not as their diabetes.

**Curriculum vitae:** David is a Researcher and Lecturer at the University of Geneva. His areas of expertise are global health, health management, access to medicines, diabetes, chronic diseases and health systems. Before joining the University of Geneva David was the Project Coordinator of the International Insulin Foundation (IIF) based at University College London (UCL) where he developed and implemented a health systems tool to assess to access to diabetes care in six countries.

David obtained his MSc in Public Health at the London School of Hygiene and Tropical Medicine. For his Masters' dissertation, he worked at the WHO looking at ways of preventing Type 2 diabetes in children. David has completed his PhD in 2011 looking at the needs of people with Type 1 diabetes in 13 countries.

# Psychological Interventions

## INV02

### microRNAs in Pancreatic Beta Cells: From Cradle to the Grave

A. Hardikar, on behalf of RAPID Study group
*University of Sydney, NHMRC Clinical Trials Centre, Sydney, Australia*

Ever since the discovery of small non-coding RNAs, microRNAs have been shown to play a critical role in development and function of pancreatic insulin-producing beta cells. Research carried out until now has clearly demonstrated that microRNAs can specifically target key pancreatic transcription factors and signalling molecules to impact on insulin production and secretion. Recent studies demonstrate that microRNAs are not only confined to cells but are also detected in several biological fluids. These data indicate that miRNAs may be looked upon as biomarkers as well as regulators of disease. I will discuss our research in understanding the role of microRNAs in pancreatic beta cell development, function and death. I will discuss the possible mechanisms that contribute to identifying the role of microRNAs as sensitive and efficient biomarkers to predict the progression of Diabetes. The findings discussed herein form the basis of the ''RAPID study'' that we started to predict islet cell death in human populations. Understanding the signatures of microRNAs / ncRNAs that are involved in genesis of pancreatic β- cells would provide more information of their progression to the ''grave'', especially in children with type 1 diabetes.

**Curriculum vitae:** Anand Hardikar, PhD is an Associate Professor and an Australian Future Fellow (ARC) at the NHMRC Clinical Trials Centre, University of Sydney. The major focus of his lab is to understand the role of microRNAs in development and function of insulin-producing cells and their role as a biomarker as well as regulators of disease progression. He is on the editorial board of 4 international journals related to microRNAs and islet biology. He is a vice-president of the Islet Society, Stockholm, Sweden and a visiting scientist at the National Centre for Cell Science, Pune, India.

## INV03

### Diabetes in Body and Mind: The Problem of Insulin Omission

J. Haug
*Oslo Diabetes research Center, Oslo, Norway*

Diabetes Type 1 has specific psychological implications valid for every person with the disease. The psychological implications can be deduced directly from the somatic characteristics of the disease, and will create processes that combine body and mind. The diabetes specific processes are insolubly connected to the fact that the production and the regulation of insulin no longer is an automatic, hidden mechanism not experienced in the conscious state. The person need to develop a new self-guiding and regulating system for insulin injections which works despite the fact that the body give inadequate signals which could be used to indicate insulin requirements at all times.

The significance and meaning which insulin has for young people with Diabetes Type 1 is therefore of vital importance for the metabolic control. In clinical practice it has proved very yielding to map the emotional aspects and attitudes related to the youngsters' conceptions about insulin. When a young knowledgeable girl omits insulin injections on her own free will, the reason might be that she uses the omission as a slimming method. Strong motivating forces against becoming fat can weaken the intellectual understanding that she need insulin. For others, insulin injections can awaken fearful conceptions regarding hypoglycaemia and for that reason overshadow the understanding for the physiological need for insulin. Aggressive impulses towards the controlling significance of insulin injections can also for some be the prime motive for omission. The main point is that intellectual understanding has limited value if strong emotions of negative character are connected to the injections. It is therefore a great challenge for health care professionals to initiate an intervention that helps young people to establish positive attitudes towards the specific psychological implications connected to the treatment of the disease.

**Curriculum vitae:** Jon Haug, educated as a specialist in clinical psychology in Norway.

Worked with diabetes, both in clinical practice and in psychological research on diabetes for 30 years.

Member of The Norwegian Diabetes Association Medical board.

## INV04

### The Solution to Insulin Omission: Practical Approaches to Engaging and Motivating Young People in (their) Diabetes Care

D. Christie
*University College London Hospital NHS Foundation Trust, London, United Kingdom*

Living with diabetes can be exhausting! At times people may have the capacity to make positive choices about their lifestyle to care for their health however be so burnt-out they are neither ready or willing to make these choices. This lack of interest is frustrating for the individual, their family and healthcare professionals. Motivational Interviewing is a client centered directive counseling style that helps people explore and resolve ambivalence about changing behaviour (1). It is way of working that is thoughtful and skilful and has been found to be useful and effective in a wide range of situations. It aims to elicit internal motivation to change and can be used as a prelude to treatment and/or integrated with other treatment approaches.

It works with ambivalence and resistance that are often particularly challenging to clinicians.

The presentation will describe how to help individuals think about why they might want to take control of external forces (like illness or emotional/behavioural difficulties). This approach is helpful in working with people who are struggling with a rage of issues and are initially unwilling to engage with the psychosocial team or medical teams (2).

The presentation will present theory and practice links and the basic principles of Motivational Interviewing. Participants will have an opportunity to practice how to address ambivalence using a decisional balance exercise.

**References:**

(1) Miller, W. & Rollnick, S., (2002) Motivational Interviewing: Preparing people for change (2nd Edition) Guilford Press, London.

(2) Christie, D. (2008). Dancing with diabetes: brief therapy conversations with children, young people and families living with diabetes. European Diabetes Nursing 5(1), 28–32

**Curriculum vitae:** Dr Christie is a consultant clinical psychologist and honorary reader in paediatric and adolescent psychology at UCLH. She is an international presenter and trainer in motivational and solution focused therapies working with multidisciplinary teams to help them engage and communicate with children, young people and families.

Research includes effective multidisciplinary interventions for diabetes and obesity, quality of life and outcomes of meningitis in childhood. Awards: Adele Hoffman Visiting Professorship in Adolescent Medicine and Health (2013) Outstanding Scientific Achievement in Clinical Health Psychology (2004) Association for the Study of Obesity Best Practice award (2001) Diabetes Award in Adolescent Health (2001). Published over 90 peer reviewed papers and chapters.

# JDRF / ISPAD Symposia | Microbiota and Type 1 Diabetes

INV05

## The Role for the Gut Microbiota in Type 1 Diabetes: Early Evidence from Humans and Animal Models of the Disease

M. Atkinson
*The University of Florida, Pathology and Pediatrics, Gainesville, FL,USA*

The incidence of type 1 diabetes (T1D) has been increasing worldwide, indicating the presence of one or more major environmental factors affecting the pathogenesis of the disease. This increased incidence is most marked in children ages one to five years, suggesting that immunoregulation in childhood has been altered. A key question for this field has been, and remains, ''What underlies this environmentally based risk for T1D?'' Based on the hypothesis that immunoregulation in childhood arises from the symbiotic relationship of the host with the intestinal microbiota, we have explored the concept that alteration in the intestinal microbiota is predisposing to childhood onset T1D. Recent evidence from the NOD mouse model of T1D suggests that the microbial environment, particularly the intestinal bacterial flora, may play a role in modulating the autoimmune pathogenesis of T1D. This, through evidence both indirect (antibiotic treatment) to direct (administration of specific bacteria) that alter both disease frequency and immune responses. Animal models represent the extreme of a controlled environment and while certainly valuable, additional efforts in humans are clearly necessary. To that end, limited data thus far attained in humans mimics (in a way) efforts in NOD mice, suggesting a potential role for specific microbiota in association with the pathogenesis of the disease. The primary source for microbiome studies, including analyses such microbial sequencing, involves investigation of stool samples. In this presentation, information will be provided addressing the question of what microbial communities are positively or negatively associated with T1D humans with and at varying levels of risk for type 1 diabetes, as well as data regarding potential genographic variances (i.e., country by country) in microbiota that may influence disease. In sum, while early as a discipline, evidence is mounting to suggest a potential link between the gut micobiota and T1D.

**Curriculum vitae:** The author of over 275 publications, Dr. Atkinson is beginning his 28th year of investigation into the field of type 1 diabetes (T1D). He has recieved multiple scientific and humanitarian based awards for these efforts. He has provided leadership to the T1D community through service with the JDRF, ADA, NIH and other organizations. Dr. Atkinson is an internationally recognized authority on multiple aspects pertaining to T1D, including disease prediction, the role for environment in T1D, stem cells and pancreatic pathology, gut microbiome, and identifying markers of tolerance and immunoregulation. He is also active with humanitarian causes, including attempts to increase awareness and support for international based efforts that bring food/medications/education to third world countries.

INV06

## Can Type 1 Diabetes be Prevented by ``Healthy'' Gut Microbiota-Induced Immunoregulation?

R. Insel
*JDRF, New York,USA*

The increasing incidence, earlier age of onset, and increased susceptibility of HLA moderate/low risk groups in childhood-onset type 1 diabetes (T1D) suggest that defective immunoregulation, which underlies T1D, may be occurring in early childhood more frequently than in the past. Development of the immune system and immunoregulation occurs in the neonate and infant through interaction between the developing gut microbiota and the immune system. The infant gut microbiota is susceptible to marked perturbations with less stability than the adult gut micriobiota. The mode of delivery (C-section vs. vaginal), diet (breast milk, cow's milk formula, solid food), or exposure to antibiotics or infectious agents can alter the microbiota during early childhood. JDRF is supporting investigation of the hypothesis that the rising incidence and increased susceptibility in childhood-onset T1D is due to defective or altered development of ''healthy'' microbiome-induced immunoregulation. Efforts are underway to characterize the developing microbiota in childhood and how it signals ''healthy'' immune development and immunoregulation and whether this is altered in childhood-onset T1D. To prove this hypothesis and to effectively develop preventive strategies based on these studies will require a comprehensive systems biology analysis to interrogate simultaneously the gut microbiome and metagenomics, immune system, and metabolites using longitudinal samples from genetically matched at-risk children who do and do not develop T1D. Future potential therapies for inducing ''healthy'' immunoregulation to prevent T1D may include the administration of probiotics, including genetically engineered microbes and parasites, prebiotics, synbiotics (probiotics and prebiotics), microbial molecules or metabolites, or novel chemical immunoregulatory molecules to newborns/infants and/or their pregnant mothers. JDRF is championing and supporting these lines of investigation for prevention of T1D.

**Curriculum vitae:** Richard Insel, M.D. is the Chief Scientific Officer of JDRF, the worlds' largest funder of type 1 diabetes research with an annual research budget over $100M that is focused on curing, treating, and preventing type 1 diabetes. Prior to joining JDRF in 2003, Dr. Insel was founding Director of the Center for Human Genetics and Molecular Pediatric Disease and Professor of Pediatrics and Microbiology/Immunology at the University of Rochester Medical Center. During his 26-year affiliation with the University of Rochester Medical Center, he also held several positions including Acting Chair of Pediatrics, Director of the Strong Children's Research Center, and Chief of the Division of Pediatric Immunology, Allergy, and Rheumatology.

# Biomarkers and Pathogenesis of Diabetes Complications

INV07

## From Glycation to Advanced Glycation and Back

K.F. Hanssen
*Department. of Endocrinology, Department of Medicine, Oslo, Norway*

Hyperglycemia is the driving force behind micro and partly macrovascular complications in diabetes, but the mechanism is not well understood. There are five interrelated pathways of interest:sorbitol, hexosamine, protein kinase C, oxidative stress and advanced glycation endproducts (AGE) (Brownlee). Glycation is the non-enzymatic reaction between glucose or other carbonyls with terminal amino acids to Amadori (e.g., glycated hemoglobin (HbA1c). AGE's are formed mostly by modifications of Amadori products by condensation, oxidation. The modified proteins have changed functions, making it more ''stiff'' in the vessel wall and heart, binding to receptors (RAGE and scavenger). Methylglyoxal (from glycolysis) modifies proteins: Methylglyoxal derived hydroimidazolone (MG-H1) has increased levels in serum and vitreous fluid in retinopathy. Methylglyoxal is broken down by glyoxalase. Overexpressing glyoxalase shows amelioration of retinopathy Modification of LDL by methylglyoxal leads to more atherogenic small LDL. Carboxymethyllysine (CML) modified proteins binds to RAGE receptors and are elevated in serum in children with type 1 diabetes many years before they develop late complications. The crosslinker Glucosepane is more tightly linked to mean glucose than other AGE's. Inhibition of glycation and hence of complications by different compounds have been achieved in animal models, but not in man. Reanalysing DCCT data showed that present retinopathy status is more of an reflection of the HbA1c level about 3–8 years earlier underlining the long term ''memory'' of high glucose. This calls for good blood glucose control from the start of the disease

**Conclusion:** Glycation and advanced glycation are linked to complications in type 1 diabetes. MG-H1 has an important role in diabetic retinopathy. Glucosepane is a prognostic marker for microvascular complications in DCCT. Amadori products may not only be a good marker of glycemic control, but may be involved in pathogenesis.

# VIDIS Symposium | Viruses and Diabetes

INV08

## Islet Inflammation, Viral Infection and Innate Immunity in Type 1 Diabetes

F. Dotta[1], I. Spagnuolo[2], G. Sebastiani[1], A. Patti[1] & F. Grieco[2]
[1]*University of Siena, Siena, Italy;*[2]*Fondazione Umberto Di Mario ONLUS, Siena, Italy*

A complex scenario characterizes the immunopathogenesis of beta cell destruction in type 1 diabetes (T1DM), with several interactions among genetic, environmental, immunological and metabolic factors. A further contribution to this complexity is provided by heterogeneity of pathogenic mechanisms among different patients. Such heterogeneity regards the strength of the autoimmune attack and, as a consequence, the residual β cell mass at diagnosis. In such a scenario increasing evidence has shown that viruses may, on one side infect pancreatic β cells thereby inducing β-cell dysfunction and contributing to islet inflammation and damage or, on the other, may modulate the immune response. In the light of such a correlation and of the above-mentioned heterogeneity in T1DM pathogenesis, the existence of a single viral strain to be considered as ''the diabetogenic'' virus seems unlikely; rather, in a given individual, a specific viral infection may determine β-cell dysfunction, thus favoring progression to overt diabetes in the presence of an anti-islet autoimmune process otherwise not able, per se, to cause disease development. Alternatively, a viral infection may influence immune regulation and anti-islet immune response at different levels, thus contributing to the level of aggressiveness of the autoimmune process.

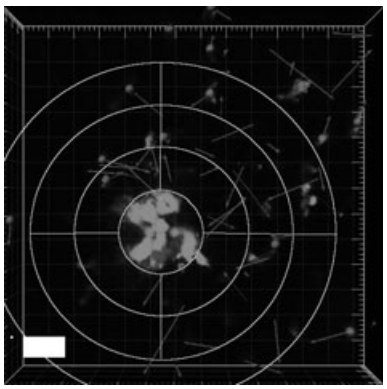
In summary, several studies have confirmed that viruses, and particularly enteroviruses, may indeed participate to T1DM pathogenesis, although their effective role is strongly influenced by the genotype of the host, the serotype of the virus, the timing of infection and the characteristics of the ongoing autoimmune response. Collaborative studies and research networks, such as nPOD or VIDIS, aimed at creating biobanks and at favoring collaborations among researchers, will be needed to address the several open questions that, so far, still remain unanswered.

INV09

## How anti-viral CTLs seek and destroy beta cells in type 1 diabetes

K. Coppieters[1], N. Amirian[2] & M. von Herrath[2]
[1]*Ghent University, Ghent, Belgium;*[2]*The La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA*

Evidence is mounting in support of a role for viral infections in the initiation of islet autoimmunity and progression to clinical type 1 diabetes. Imaging diabetogenic immune responses *in vivo* at cellular resolution within pancreatic islets has been an elusive goal. The majority of work has focused on strategies to non-invasively quantify β- cell mass during natural disease progression, experimental therapy and islet transplantation. We have designed a novel technique that allows for the *in vivo* visualization of diabetogenic CD8 T cell responses within mouse pancreatic islets. This approach was employed to determine the dynamical behavior of a CD8 T cell population that is activated and expanded as a result of a peripheral viral infection. We found that upon viral clearance, these cells primarily arrest in the postcapillary vessels in close proximity to the pancreatic islets. Following extravasation, the diabetogenic CTL efficiently migrate through the exocrine pancreas and are able to traffic between anatomically nearby islets. We found that the islet-infiltrating CD8 T cells rarely arrest or contact beta cells directly yet show confined motility. Finally, induction of beta cell death required the presence of hundreds of CTL in the immediate vicinity of an islet. Collectively, these data offer direct insight into the infiltration kinetics of virally expanded CD8 T cells in pancreatic islets during autoimmune diabetes development.



INV10

## Type 1 Diabetes in the Tropics: Do Viral Infections Enhance or Protect Diabetes?

L. Sarmiento
*Pedro Kouri Tropical Medicine Institute, Virology, Havana, Cuba*

In Cuba, meningitis epidemics due to echovirus (E) 4, 16, and 30 have been documented in 1986, 2000, and 2001, respectively. One of the most notable observations from these HEV epidemics is that in the convalescent but not in the acute stage of the infection, islet cell antibodies (ICA) seroconversion was demonstrated. The prevalence of ICA during the 2000 and 2001 meningitis epidemic was as high as 92% and 87%, respectively; however, ICA prevalence was moderate (36.1%) in the 1986 epidemic. It was shown that the strains of E16 and E30 isolated from Cuban epidemics during the years 2000 and 2001, respectively display a remarkable tropism for human islet resulting in marked cytotoxic effects, impaired insulin secretory ability and expression of pro-inflammatory cytokines and chemokine in Islets. In contrast, E4 did not cause any effects on islet cells. Accordingly, the differential post-echovirus islet autoimmunity occurred during the epidemic in Cuba might be a result either of differences in the ability of the viruses to induce pro-inflammatory innate immune activation in islets or a differential islet cell killing capacity of the viruses. On the other hand, a significantly higher frequency of enterovirus RNA in serum from type 1 diabetes children at the onset of disease, as well as in ICA positive first-degree relatives compared to healthy control subjects was demonstrated. Although the prevalence of ICA in the children infected with E16 and E30 was as high as 92% and 87%, respectively, no patient positive for ICA/related autoantibodies during the original epidemics developed T1D 10 years later.

According to these observations, it is reasonable to assume that while the β- cell autoimmunity may be triggered upon exposure to diabetogenic enterovirus, the regulatory mechanisms could halt islet destruction and eventually abort the autoimmune process. Further studies are needed to assess the capability of enterovirus to generate protective immune mechanism in human.

# Diabetes Care in School

INV11

## Diabetes Program at School In Turkey

S. Hatun
[1]*Kocaeli University Medical School, Pediatric Endocrinology, Kocaeli, Turkey*

**Background:** There are approximately 20 000 diabetic children in Turkey, who are mostly at school ages and it is possible to solve the problems by means of a comprehensive program. Diabetes Program at School is developed by the Turkish Society of Pediatric Endocrinology and Diabetes in cooperation with the Ministry of National Education and Ministry of Health. The program has three objectives: (1) Raising awareness about Type 1 Diabetes by means of teachers, (2) Strengthening the diabetic child's care at school ages, (3) Generating a healthy nutrition attitude among school children and raising awareness about obesity.

**Activities:** An awareness poster under the title ''Is my child a diabetes patient?'' is now on the walls of schools across Turkey. It has reached to approximately 650 000 teachers and 16 million school children at primary and middle schools. Access to a brochure on diabetes in childhood, a guide on diabetic child care at school and a presentation on the training of teachers has been provided on related web pages. Pediatric Endocrinology Clinics across the country began to send a standardized letter on the diabetic child's care at school to diabetic children and their teachers. School children (7 500.619 children) and teachers (583.182 teacher) have jointed the school trainings to be organized within the scope of Diabetes Program at School and two films with a total duration of 24 minutes runed at 24 836 schools, where the issues related to Diabetes and obesity among children are explained. For this reason, a training platform is generated on the website www.okuldadiyabet.org to access educational material.

**Conclusion:** The signs and symptoms of diabetes in children were told the teachers, students and community, strongly. The problems faced by diabetic children in school were pointed out. Permanent education materials about diabetes and obesity were created for the teachers and students.

INV12

## POLICY AND LEGISLATION: Safe at School for Children with Diabetes: From Policy to Practice

L. Siminerio
*University of Pittsburgh Diabetes Institute, Medicine, Pittsburgh, United States*

Safety can be a concern for students with diabetes at school when there is no one available to perform emergency and routine diabetes care tasks. Using a four-pronged approach to advocacy that includes education, negotiation, litigation, and legislation, the American Diabetes Association's Safe at School Campaign is a model for advocating for a medically safe school environment. This includes the right to self-care and access to trained personnel who can provide both emergency and routine care to students with diabetes. While much of the Association's school advocacy efforts have been focused upon educating parents about their legal rights and developing negotiation tools to secure appropriate care for their children in the school setting, the Association has been successful in passing school diabetes care laws in a number of states to make sure that there are trained school personnel available to provide assistance to students with diabetes and that laws and diabetes care protocols are applied consistently throughout the state. The Association's Safe at School campaign relies on the expertise, skills, and talents of health care professionals, attorneys, school nurses, educators, parents, and other advocates to achieve successful implementation of state school diabetes care laws. This session will briefly discuss the challenges faced by students with diabetes and their families and their legal rights, how the Association has employed its strategy of educate, negotiate, litigate, and legislate to effectuate policy change, and how this approach has resulted in improved care for many students with diabetes.

# The Brain and Glucose Metabolism incl. Lestradet Award Lecture

INV13

## Another Piece of the Jigsaw: How the Brain Regulates Pancreatic Endocrine Function

R. McCrimmon

*University of Dundee, Cardiovascular and Diabetes Medicine, Dundee, United Kingdom*

The critical importance of glucose as a fuel to meet whole body energy demands ensures that multiple mechanisms are in play to ensure that glucose levels are tightly maintained. Specialised cells that detect changes in glucose are present in the central nervous system and periphery and together form an integrated network tasked with preserving glucose homeostasis. As an example of this, this presentation will focus on brain-endocrine axis. A significant body of research has demonstrated a direct regulatory role for brain glucose-sensing neurons via the autonomic nervous system of pancreatic β- and α-cell function. These studies suggest that impaired glucose homeostasis, such as is associated with type 2 diabetes, as well as the loss of α-cell glucagon release during hypoglycaemia in type 1 diabetes, may in part result from changes in central glucose sensing neurons. These findings may offer new approaches to the treatment of diabetes in the future.

**Curriculum vitae:** Rory McCrimmon trained at the University of Edinburgh and completed his clinical and speciality training in the South-East of Scotland. In 2002, he joined the faculty at Yale University to develop his basic research in the central regulation of glucose homeostasis. In 2009, he was appointed as Clinical Reader in the University of Dundee. Dr McCrimmon's Laboratory focuses on the basic mechanisms through which the brain detects developing hypoglycaemia. His laboratory has made a number of important contributions to this field and the work of has laboratory as been presented at many national and international meetings.

INV14

## Neural Circuits in Hypoglycemia Counterregulation

A.M. Arbelaez

*Washington University, Division of Pediatric Endocrinology, Saint Louis, United States*

Hypoglycemia is the limiting factor in the glycemic management of diabetes mellitus (DM). It causes recurrent morbidity, affecting the activities of daily living and 6–10% of the deaths of people with T1DM have been attributed to hypoglycemia. Furthermore, recurrent hypoglycemia causes both defective glucose counterregulation and loss of hypoglycemic symptoms during subsequent hypoglycemia, constituting the clinical syndrome of hypoglycemia-associated autonomic failure (HAAF). The mechanisms underlying sympathoadrenal responses during hypoglycemia and the loss of these responses during HAAF are thought to involve the brain.

Orchestration of these responses by the brain is a complex phenomenon, given that each brain region is distinct in its functions and connections. Data from my lab and others suggests that there is a cerebral network of interconnected brain regions that are implicated in the modulation of hypoglycemic visceral and autonomic responses in humans. Alteration in the signaling of these regions seem to be involved in the attenuation of the sympathoadrenal and symptomatic responses that occurs in HAAF.

Compelling evidence demonstrates that the brain is a very metabolically active organ, but the influence of brain metabolism on physiologic responses during hypoglycemia is poorly understood. It had been long believed that the energy needed for brain function was produced entirely by glucose oxidation, but more recent data suggest that in certain physiologic states the brain can use fuels other than glucose from the circulation, particularly if their levels rise high enough to enter the brain.

We envisage that a detailed understanding of how the brain orchestrates these neural signals and metabolic changes to hypoglycemia will be instrumental for optimal design of novel intervention strategies to minimize or prevent iatrogenic hypoglycemia.

**Curriculum vitae:** Dr Arbelaez attended medical school at the Universidad del Valle in Cali-Colombia and went to the United States to complete a pediatric residency at Washington University. She then pursued subspecialty training in Pediatric Endocrinology under the mentorship of Dr Philip Cryer and earned a Master's Degree in Clinical Investigation. While at Washington University she has served as Co-Investigator for the Cooperative Multicenter Diabetes Research Network for Hypoglycemia Prevention-DirecNet-2 and TODAY study.

Her research focuses on a novel intersection between the field of clinical neuroscience and endocrinology using innovative imaging techniques to better understand the role of the brain on the physiology of glucose counterregulation in humans.

# Nutriton

## INV15
### Glycemic index

J. Brand-Miller
*University of Sydney, Sydney, Australia*

Current diabetes management guidelines recommend carbohydrate counting to adjust mealtime insulin in children and adults with type 1 diabetes. Surprisingly, these recommendations are based simply on a grading of the available evidence. There is no high quality meta-analysis to quantify the effect of carbohydrate counting on HbA1c. The theoretical basis of carbohydrate counting is also questionable because the same amount of carbohydrate from a given food or meal can produce 2 or 3-fold differences in postprandial glycaemia. The glycemic index of foods is a tool that systematically ranks carbohydrate exchanges according to the glycemic response in healthy individuals. A database of over 2000 foods and their GI values can be found online (www.glycemicindex.com). In children with type 1 diabetes, meals with the same carbohydrate content but different glycemic index have been shown to produce markedly different glucose profiles. Long term (12 month) dietary management with the glycemic index improved HbA1c significantly compared with the use of carbohydrate exchanges in Australian children with type 1 diabetes, without increasing the rate of hypoglycemia. In the families exposed to both carbohydrate counting and flexible low GI instructions, quality of life was rated higher when usiing the GI. In young people using CSII, the GI influences the optimal bolus type. Compared with the standard bolus, a dual wave bolus before low GI meals decreased postprandial area under the curve by ~50%, and lowered the risk of hypoglycemia for the same premeal glucose concentration. Compared with standard high fibre diets, low GI diets also improved weight control, cardiovascular risk factors and number of medications in individuals with type 2 diabetes and/or overweight. These findings provide a rationale for using glycemic load (carbohydrate content x GI/100) in place of carbohydrate counting to estimate the insulin bolus in individuals with type 1 diabetes.

## INV16
### Sport & Diabetes:Nutritional Challenges for Young Athletes

F. Annan
*Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom*

Sports nutrition has a recognised role in the lives of adult athletes. A sound diet is an intergral part of training for sports performance. Sports nutrition guidelines such as the Joint Position Statement on Nutrition and Athletic Performance (ACSM, 2009) exist for adult competitors, and are well recognised documents guiding practice. Paediatric sports nutrition is less well established with many of the recommendations on the composition of the diet taken from adult guidelines.

Young competitors need a diet that is adequate to fuel both training and the demands of growth. Fitting appropriate food choices into a busy life can be challenging. The young athlete with diabetes has the additional burden of trying to achieve glycaemic control whilst eating to fuel athletic performance. Food intake needs to meet the demands of training and recovery, as well as limiting problems that may occur due to nutritional deficiency and injury (Meyer et al 2007, Jeukendrup & Cronin 2011).

This presentation will share with you some experiences of working with young athletes with diabetes and consider nutritional and educational strategies that can be employed to help them cope with the challenges they face.

American College of Sports Nutrition,American Dietetic Association, Dietitians of Canada, Joint Position Statement: Nutrition and Athletic Performance 2009, Medicine & Science in Sport & Exercise Science, 709–731

**References:**

Meyer F., O'Connor H., Shirreffs S.M. Nutrition for the young athlete. J Sports Sci.2007;25:73–82.

Jeukendrup A., Cronin L. Nutrition and elite young athletes. Med Sports Sci. 2011;56:47–58.

## INV17
### Nutrition in Toddlers and Young Children with Diabetes

S. Patton
*University of Kansas Medical Center, Pediatrics, Kansas City, United States*

Diet is an important component of diabetes management, underpinning all other daily diabetes self-care behaviors (e.g., insulin, monitoring, and exercise). Proper dietary management of type 1 diabetes includes accurate carbohydrate counting and attention to healthy eating by consuming a variety of foods from different food groups and limiting intake of dietary fat. In toddlers and young children with type 1 diabetes, achieving optimal dietary management may be a particularly important goal because young childhood is a period when children are developing food preferences and may be amenable to behavior change. The focus of this presentation will be on diet and healthy eating in toddlers and young children with type 1 diabetes. Research will be presented to describe how families of young children with type 1 diabetes are doing consuming a healthy diet, the barriers families may perceive to healthy eating, and relations between healthy eating and glycemic control. Recommendations will be discussed regarding strategies to teach families how to plan for and encourage healthy meals and how to manage child food refusal and/or other disruptive behaviors at mealtimes.

# Unusual Forms of Diabetes: Basic Science and the Role of Registries

INV18

## The ISPAD Rare Diabetes Collections: Neonatal Diabetes and Beyond

A. Hattersley
*Peninsula Medical School, Exeter, United Kingdom*

The ISPAD rare diabetes collection was set up after a chance meeting over breakfast in Mexico in 2000 between Andrew Hattersley and Jan Bruining. The ISPAD rare diabetes collection was a ''dating agency'' aimed to bring together paediatricians who had patients with genetic types of diabetes but didn't know how to get genetic testing with basic scientists who did not have access to patients.

The ISPAD rare diabetes collection led directly to the definition of the major genetic causes of neonatal diabetes. The discovery that neonatal diabetes was commonly caused by potassium channel mutations and these patients blood glucose was better controlled by sulphonylurea tablets rather than their insulin injections has transformed clinical care in neonatal diabetes Now a direct neonatal diabetes service (www.diabetesgenes.org) has been set up offering a free diagnostic service for all patients diagnosed under 9 months. As well as resulting in over 500 patients having excellent control after discontinuing insulin it has also meant that we now understand the cause of 20 different types of neonatal diabetes with different associations and treatment requirements.

There are still patients with novel genetic syndromes where we do not understand the cause. Defining the causes can give new insights into the cause, clinical syndrome and potential for treatment. The most recent discovery was finding the commonest cause of pancreatic agenesis is due to *GATA6* mutations and is almost always associated with cardiac mutations and other developmental disorders. This discovery may be of use in work attempting to produce cell therapy from stem cells for people with type 1 diabetes.

No-one could have predicted the success of the ISAPD rare diabetes collection and we are very grateful for everyone who has supported it over the last decade. Please contact us if you have any questions about genetic testing for any neonatal or syndromic patients.

INV19

## Euro-WABB: A Disease Specific Registry for Wolfram, Alstrom and Bardet-Biedl Syndromes

T. Barrett
*University of Birmingham, School of Clinical and Experimental Medicine, Birmingham, United Kingdom*

Rare diabetes syndromes are under-recognised; delayed diagnosis is common; treatable complications may not be identified; there is a lack of management guidelines; and it is challenging to recruit sufficient patients to clinical trials. Wolfram (childhood onset diabetes mellitus, optic atrophy), Alstrom (infancy onset obesity, retinal dystrophy and insulin resistant diabetes) and Bardet Biedl (polydactyly, infancy onset obesity, retinal dystrophy and insulin resistance) and other rarer syndromes are uncommon (less than 1:100 000), linked by vision loss and deafness, and all develop diabetes mellitus by adulthood. We aimed to establish a Registry to address these issues.

Our consortium includes scientific and clinical experts in each of these syndromes. We agreed a common dataset of clinical, investigation adn molecular diagnostic data to distinguish between the syndromes and provide a searchable database for researchers. We also incorporated data fields for Wolcott-Rollison, Thiamine-Responsive Megaloblastic Anaemia, Diabetes and Deafness, and other rare diabetes syndromes. We wrote an ethics submission template for national approvals, to include consent to link national and international registries. We designed a web based registry with build in security for data confidentiality, anonymised data collection, and facility for patients to self register. We linked all molecular diagnostic laboratories offering genetic testing for these syndromes. Finally we designed a website for dissemination of information to health professionals and families.

The core dataset includes 44 data fields which define and separate the syndromes; the extended dataset includes 370 data fields for detailed phenotyping. We currently have ethics approval in 7 EU states, and the first 140 patients recruited. This Registry will improve patient services, health professional awareness, and allow recruitment into multi-national clinical trials. Further details can be found at www.euro-wabb.org

# Type 2 Diabetes in Youth: Results from the TODAY Study

## INV20

### Type 2 Diabetes (T2D) in Youth: Results from the TODAY Study

L. Laffel, TODAY Study Group
*Joslin Diabetes Center Harvard Medical School, Boston, United States*

**Objectives:** In response to the epidemic of childhood overweight/obesity and T2D, TODAY, the largest clinical trial to date of youth with T2D, investigated 3 treatment regimens aimed at achieving durable glycemic control in children and adolescents with T2D of recent onset.
**Methods:** At 15 US sites 699 youth ages 10–17 years old with T2D <2 years duration (mean 7.8 months) were randomized among 3 treatments: metformin (1000 mg BID; M); metformin plus rosiglitazone (4 mg BID; M + R); metformin plus a lifestyle intervention (M + L) focused on weight loss through healthy eating and physical activity. Participants were followed for 2–6 years (mean 3.9). The primary outcome was A1c ≥ 8% for 6 months or metabolic decompensation requiring insulin therapy. Targeted weight loss was 7% reduction in percent overweight at 6 months.
**Results:** Almost half (45.6%) reached primary outcome. M + R was superior in maintaining durable A1c compared with M (38.6% vs. 51.7% failure, P = .006). M + L was intermediate and not significantly different from the other groups. There were differences in treatment outcomes by sex and race: M had the least efficacy in non-Hispanic Blacks; M + R was more effective in females than males. In M + L 31.1% achieved the goal of at least 7 percentage points reduction in percent overweight at 6 months; this differed significantly from M + R (16.7%, P <0.001) but not from M (24.3%). BMI differed significantly across time by treatment; M + R participants experienced the greatest BMI increase and M + L the least, however, BMI was not a determinant of treatment failure. Overall, 19.3% reported serious adverse events.
**Conclusions:** M monotherapy maintained durable glycemic control in ~50% of youth with T2D; M + R increased the proportion maintaining durable A1c levels by 25%. Despite the more positive impact of M + L on weight, A1c outcomes were intermediate. Additional study is needed to assess long-term outcomes in the TODAY cohort.

## INV21

### Treatment Effects on Insulin Sensitivity and b-cell Function in TODAY

S. Arslanian, TODAY Study
*Children's Hospital of Pittsburgh of UPMC, Pittsburgh, United States*

**Objectives:** TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) demonstrated that combination therapy with metformin plus rosiglitazone provided superior durability of glycemic control compared with metformin alone with significantly lower treatment failure rates (38.6% vs. 51.7%), while metformin plus lifestyle was intermediate (46.6%). Herein, we describe the temporal changes in measures of β-cell function and insulin sensitivity from an oral glucose tolerance test (OGTT) over a 4-year period among the three treatments.
Methods: TODAY participants (699), 10–17 years. old, with type 2 diabetes of <2 years duration were treated for a median of 2.47 years with metformin alone, metformin plus rosiglitazone, or metformin plus lifestyle and underwent periodic OGTT testing.
**Results:** Measures of insulin sensitivity [1/fasting insulin ($1/I_F$)] and β-cell function relative to insulin sensitivity [oral disposition index (oDI), product of insulin sensitivity and insulinogenic index ($rI_{30}/rG_{30}$) or ($rC_{30}/rG_{30}$)] showed more favorable changes over time with metformin plus rosiglitazone vs. metformin alone vs. metformin plus lifestyle. In those who failed to maintain glycemic control, β-cell function was significant lower (~50%) at randomization compared with those who did not fail, with continued marked deterioration.
**Conclusions:** The beneficial change in insulin sensitivity and the consequent decrease in secretory demand on the β-cell with metformin plus rosiglitazone appear to be responsible for its superior glycemic durability over metformin and metformin plus lifestyle. In addition however, initial β-cell reserve and degree of glycemic control at randomization are significant determinants of treatment failure and the ability or lack thereof to maintain glycemic control. Therefore, earlier interventions, before significant loss in β-cell function occurs, may prove beneficial in the treatment of youth with type 2 diabetes.

## INV22

### Burden of Comorbidities in Youth in the TODAY Trial

L. Levitsky, TODAY Study
*MassGeneral Hospital for Children, Boston, United States*

**Objectives:** To describe medical conditions, events, diagnoses, diabetes comorbidities and precursors in TODAY subjects with youth-onset type 2 diabetes (T2D).
**Methods:** N = 699 youth (10–17 years) with T2D diagnosed <2 years were randomized to 3 treatment groups: metformin alone, metformin + rosiglitazone, and metformin + lifestyle intervention. They were followed for 2–6.5 years (mean 3.8 years) and had regular measures of HbA1c, lipids, liver function, and renal function,as well as documentation of blood pressure and body weight changes. At end of study, fundus photographs and echocardiograms were obtained.
**Results:** At baseline 11.6% were hypertensive (BP $^{3}$95th percentile or systolic ≥130 or diastolic ≥80), 3.3% had elevated LDL (≥130 mg/dL), 18.2% had elevated triglycerides (≥150 mg/dL), and 6.3% had microalbuminuria (≥30 mg/g creatinine). There were no significant differences by treatment group in new cases diagnosed over equivalent person-years of follow-up. At end of study, 33.8% had hypertension, 10.3% abnormal LDL, 28.2% hypertriglyceridemia, and 16.6% microalbuminuria. Hypertension was significantly associated with sex, age at baseline, and BMI over time. Microalbuminuria was significantly associated with HbA1c over time. Percent with high risk LDL (≥130 mg/dL or on statin or sequestrant) or high risk triglyceride (≥150 mg/dL or on fibrate) did not change over 3 years of follow-up. Echocardiography showed that participants had large hearts, an independent risk for CVD; determinants of increased left atrial size and left ventricular mass were similar to the general population (BMI and BP). Nonproliferative retinopathy was identified in 13.7% of subjects 2–8.4 years after diagnosis.
**Conclusions:** Comorbidities start early in the course of T2D in youth. Long-term follow up will assist in understanding disease progression and examine the effect of early treatment and glycemic control.

# Lessons from Countrywide Diabetes Registries and Organizing National Diabetes Programs

## INV23

### The National Paediatric Diabetes Audit: State of Outcomes for Diabetes Care in England and Wales

J. Warner
*RCPCH lead for the NPDA, Children's Hospital for Wales, Cardiff, United Kingdom*

The National Paediatric Diabetes Audit (NPDA) highlights the main findings on the quality of care for Children and Young People (CYP) with diabetes mellitus (DM) in England and Wales and has been running for 8 years. The NPDA is commissioned and sponsored by the Healthcare Quality Improvement Partnership (HQIP) following advice to the Department of Health from the National Clinical Audit Advisory Group (NCAAG) and conducted by The Royal College of Paediatrics and Child Health (RCPCH).

The NPDA covers the components of the National Service Framework for Diabetes and includes details on the number of CYP with diabetes in England and Wales, the care processes they receive and outcome measures, including inpatient admissions for diabetic ketoacidosis where applicable.

In England and Wales there are 185 centres providing in- and outpatient care for CYP with diabetes and in 2010/11 there were 23 500 submissions to the audit which represents approximately 90% of the expected number. Despite a good participation rate the submission of data on care processes remains poor and outcomes such as HbA1c have remained stable with little year on year change. There are large variations in outcome measures across centres which require investigation to tease out ''good'' and ''poor'' practice.

Results from the 2010/11 audit will be discussed during this presentation and comparisons made to the previous 7 years.

## INV24

### Do Diabetes Registries Impact Clinical Care?

R. Holl[1], M. Grabert[1], E. Schober[2] & DPV Initiative
[1]*University of Ulm, Institute of Epidemiology and Medical Biometry, Ulm, Germany,*[2]*University of Vienna, Pediatric Diabetology, Vienna, Germany*

Many registries focus on case identification for incidence / prevalence calculations, while other registries follow patients longitudinally throughout pediatric care, sometimes even until adulthood. As an example, the German/Austrian DPV registry currently includes 63 716 patients with a pediatric onset, with 127 3032 visits contributed by 231 pediatric diabetes centers.

80%–90% of patients estimated in the country are included in the registry, dependent on year and age at onset. Every 6 months, each center receives a comprehensive report, including both cross-sectional comparisons (benchmarking histograms) as well as longitudinal graphs reflecting the time-trend in the individual institution compared to the trend in all centers. Separate analyses are provided for Austrian participants only, and – in open format – for regional quality circles. According to the PDCA-cycle, a continuous feedback on process and outcome indicators, together with internal and external discussion of results, will continuously improve the quality of care provided at each institution. The DPV initiative aims at including all centers, large and small, as the potential for improvement may well be greater in the latter group.

During the last 17 years, a strong trend towards intensification of insulin therapy in pediatric type-1 patients was noted, with currently 38% of all pediatric type-1 patients on insulin pumps, but also a steady increase in the number of blood glucose measurements (on average 5/day). Improved completeness of control exams following current German/Austrian/ISPAD-guidelines is demonstrated for HbA1c, blood pressure, lipid measurements and immunology, as well as retinal and microalbuminuria exams.

Registers that include all pediatric patients, not only type-1, are a valuable tool for research on rarer forms of diabetes, which cannot be performed even at the largest single center (currently available 1468 pediatric onset type-2 and 2323 ''other types'' of diabetes).

# Diabetes and Sports

## INV25

### Intensive Treatment and Competitive Sports

P. Adolfsson
*Department of Pediatrics,Gothenburg University, Gothenburg, Sweden*

The beneficial effects of physical exercise are many, but the individual also faces difficulties as exercise is associated with hypo- as well as hyperglycemia, mainly related to the duration and intensity of the exercise.

At the clinic it is therefore important to have clear strategies pointing out not only target values before, during and after exercise, but also strategies to reach this target. A well regulated glucose control is of great importance as the hormonal response during exercise is affected by the antecedent glucose control.

During sports the intensity is often extensive during competition, but for the individual the intensities will differ a lot ahead of a competition, which means that the athlete has to find a concept for each specific type of intensity/duration.

Technology as insulin pumps and continuous glucose monitoring provide the users with opportunities to succeed having a stable glucose level before, during and after exercise, but the user have to use the technology properly in order to benefit from this.

Questions regarding exercise and diabetes are common at the clinic as exercise and competitive sports also are important parts of life. A model of coaching by downloading data from different glucose meters and insulin pumps will be discussed during the lecture.

**Curriculum vitae:** Peter Adolfsson is a M.D., Ph.D., working at the Department of Diabetes at the Queen Silvia Children's Hospital, Gothenburg, Sweden. He is also specialist in Sports Medicine and is the former responsible physician of the women national football team in Sweden.

His research field regards exercise and diabetes as well as scuba diving and diabetes. He is one of the authors of ISPAD Guidelines: Exercise and diabetes. His interest also covers pedagogic tools, technology and coaching of patients and parents by download of data.

## INV26

### Evidence-Informed Exercise Management for Type 1 Diabetes Mellitus

M. Riddell
*York University, Toronto, Canada*

Exercise is a fun and important part of healthy living for children and adolescents with type 1 diabetes. However, blood glucose management during exercise remains a major challenge for patients and their caregivers. Muscular contractions of differing intensities and duration lead to varying glucose requirements that demand complex changes to numerous circulating hormones including insulin, glucagon and the catecholamines. Unfortunately, the child/adolescent with type 1 diabetes typically lacks these coordinated responses to exercise, which frequently causes severe dysglycemia (both hypo and hyperglycemia) during the activity and in recovery. For young athletes who wish to excel at their chosen sport, this dysglycemia ultimately affects performance, and could mean the difference between victory and defeat! To successfully manage the complexities of exercise with T1D, our patients require sound advice to put the pieces of the exercise puzzle together. This lecture updates the current state of knowledge on the health benefits of exercise and provides evidence-based recommendations on insulin adjustments and nutritional requirements for exercise and sport.

## INV27

### Glycemic Response to Road Cycling in Elite Athletes with Type 1 Diabetes

P. Southerland
*Team Type 1, Atlanta, United States*

This observational pilot study evaluated 17 male elite cyclists during five multiple-day cycling events. Glycemia was assessed using CGM (DexCom SEVEN). Parameters, including power and heart rate, were assessed with a cycle-mounted power meter (SRM, Julich, DE). We report a descriptive analysis of CGM data. Five time periods were analyzed: Baseline Day (0600-2200) and Night (2200-0600), Race (during racing), 1-hour Post-Race, Race Day (0600-2200 during the event, not including racing) and Race Night (2200-0600 during the event). Subject characteristics: T1DM (n = 9, age 22 ± 4year, BMI 23 ± 2kg/$m^2$, DM duration 10.4 ± 5.7year, A1C 7.6 ± 1.0%, mean ± SD); Non-DM (n = 8, age 26 ± 6year, BMI 23 ± 2kg/$m^2$). Racing events (4.8 ± 1.6 races/event and 96 ± 64 km/race, mean ± SD) took place between May-Sept, 2011. Race CGM includes a total of 103 races (T1DM 51; Non-DM 52), covering a total distance of 9676 km (T1DM 3912; Non-DM 5764), over 252hour (T1DM 102; Non-DM 150). CGM data by time period for all racing events combined: Baseline Day (0600-2200h) Baseline Night (2200-0600h) Race 1-hour Post-Race Race Day (0600-2200h) Race Night (2200-0600h) T1DM (n=9) 137 ± 28 130 ± 26 183 ± 46 210 ± 68* 158 ± 45 123 ± 35 Non-DM (n = 8) 102 ± 7 100 ± 12 110 ± 9†‡ 130 ± 12** 98 ± 5 93 ± 8 Mean ± SD mg/dL. T1DM vs Non-DM all time periods P <0.05. *P = 0.03 vs Race Day, **P = 0.0002 vs Race Day, †P = 0.01 vs Race Day, ‡P = 0.0002 vs 1-hour Post-Race Cyclists with T1DM had higher glucose values and SD for all time periods. Glycemia tended to be higher in both T1DM and Non-DM subjects during Race and 1-hour Post-Race periods compared to non-race periods. This was likely, in part, due to intermittent anaerobic activity. Further analyses from this study, and additional studies in the lab and field, are needed to help determine optimal glycemia for maximal performance in athletes with T1DM.

# Genes and Diabetes

INV28

## Type 1 Diabetes Genetics: New Results and Old Challenges

G. Morahan

*The Western Australian Institute for Medical Research, University of Western Australia, Perth, Australia*

Recent advances in genetic research have led to the identification of over 60 loci that contribute to the susceptibility of developing Type 1 diabetes (T1D). The plethora of T1D risk genes that has been identified may be overwhelming for clinicians faced with lists of gene names and symbols that have little bearing on management; it also provides a challenge for researchers to place the genetics of T1D in a more amenable clinical context. This is a timely opportunity to assess what is currently known of the genetics of T1D, and what these discoveries may tell us about the disease itself. I will review recent developments in T1D genetics, discussing the major findings under the following themes: T1D risk gene identification and characterization; shared genetic aetiology with related diseases; and understanding disease heterogeneity. The challenge of better clinical management may be met by finding a better way to use the available genetic information.