# ABSTRACTS – ORAL PRESENTATIONS

(Ordered according to programme)

## SUNDAY, 6 OCTOBER 2013

### OPENING SESSION

*Keynote Presentations:*

**Co-evolution of African cultures and genomes: Opportunities to understand human history and health**

**CN Rotimi** (Center for Research on Genomics and Global Health, National Genome Research Institute, NIH, Bethesda, Maryland, USA)

Africa is the common birthplace of all human populations. Thus, modern humans have lived longer on the Africa continent than in any other geographical regions of the world. This long evolutionary history has led to several important cultural and genetic characteristics of the African people. Africa has the highest linguistic diversity in the world with an estimated 2,000 languages; notably, Nigeria as a nation has over 500 listed languages. Also, due to vast cultural practices (e.g., farming and diet) and uneven economic developments, African populations display considerable phenotypic variation. At the genomic level, greater genetic variation is seen in present-day Africa populations, resulting in more haplotypes, lower levels of linkage disequilibrium (LD), more divergent patterns of LD and more complex patterns of population substructure. As a direct consequence of the long evolutionary history and the extraordinarily complex history of migration among African peoples, genomic disease mapping strategies such as admixture and association may not be directly transferable to African populations. For example, two ancestral population admixture models are likely to be inadequate in disease gene mapping in African populations with complex genomic patterns of recent and ancient migration. Also, present generation of genome-wide association mapping chip arrays are not as efficient in African populations compare to evolutionary younger populations in Europe and Asia. A better understanding of the limitations of the present genome-wide arrays will facilitate the development of the next generations of arrays with higher efficiency in African populations that will increase the chance of finding disease associated genes in ongoing genomic projects in Africa including the H3Africa funded initiatives. This presentation will explore how the rich genetic, ecological, and socio-cultural diversity of African populations favors the detection of selection signals shared by diverse human groups and signals that are targeted by local-specific selection pressures with the potential to advance our understanding of human migration and adaptive history. Finally, examples will be provided to demonstrate how, on the one hand, the reduced LD in African populations facilitates fine-mapping of disease associated loci and on the other hand how it presents significant challenges (e.g., increased sample size) at the discovery and replication phases of association studies.

## Building bridges in genetics: from patient to genome and back again

**CMA Van Ravenswaaij-Arts** (Dept. of Genetics, University Medical Centre Groningen, University of Groningen, The Netherlands)

The landscape of clinical genetics is changing rapidly. New diagnostic possibilities have broadened the indications for genetic counselling and testing from a limited set of congenital anomalies and developmental delay to a much wider range of conditions (including neurogenetics, cardiogenetics, oncogenetics, and pharmacogenetics), and we are now moving towards the new arena of personalised genetics. In the field of dysmorpholgy, there is a dramatic change from phenotype-first to genotype-first taking place. This change had already begun when genome-wide array diagnostics was introduced, but has become more evident with the introduction of whole-exome sequencing. However, this does not mean that clinical geneticists, and more specifically dysmorphologists, are no longer needed in the process of genetic diagnostics. They are important for building the bridges between the different players in genetics and counselling. In my presentation I will illustrate the impact of the introduction of new techniques on the diagnosis and counselling of children with congenital anomalies and developmental delay. We will make a rapid journey from chromosomes, FISH, and genome-wide array analysis to exome sequencing. New high-resolution techniques not only result in more certain diagnoses, but also in more and more so-called risk factors being identified. Unravelling the contribution of copy number variants and mutations with minor effects to specific phenotypes will require the collection of large numbers of array and exome results in combination with detailed and accurate phenotype information. In addition to yielding some unclear results, the new genome-wide techniques may also present unsolicited findings. The challenge is how best to introduce these techniques into routine diagnostics, while taking the needs and preferences of patients, care-givers and doctors into account. This is only possible if good communication, with accurate exchange of information between patients, doctors and laboratories, is guaranteed and can bridge everyone’s needs. We, as genetic professionals, can help build these bridges in genetics.

# MONDAY, 7 OCTOBER 2013

## CLARIFYING COMPLEXITY

*Keynote Presentation:*

**Insights into the genetic basis of ocular (uveal) melanoma.**

**AM Bowcock** (Imperial College, London, United Kingdom)

Metastasis is a defining feature of malignant tumours and is the most common cause of cancer-related death. However, the genetics of metastasis are poorly understood. Uveal melanoma (UM) is the most common primary cancer of the eye and the second most common form of melanoma. UMs have a highly characteristic pattern of metastasis to the liver that is resistant to conventional chemotherapy and is usually fatal. UMs have remarkably little genomic instability, few cytogenetic alterations, and rare genetic mutations. Thus, when mutations are found in these tumours, they are highly likely to be driver rather than passenger mutations. We were the first group to apply exome capture followed by massively parallel sequencing to identify BRCA1 associated protein 1 (BAP1) as the metastasis suppressor mapping to chromosome 3 in UM. BAP1 is mutated in ±84% of UMs that metastasize, and its loss in UM cell lines leads to many features of metastatic cells including acquisition of stem-like qualities through loss of differentiation. We have also identified splicing factor 3B subunit 1 (SF3B1) as a second genetic driver of UM. SF3B1 is commonly mutated in ±30% of UMs at residue R625. These alterations confer less likelihood of metastasis. We are also examining the role of SF3B1 in tumourigenesis by inspecting transcripts in tumours and transfected cells for alterations in abundance and splicing in the presence of SF3B1 alterations. Information on these and additional novel molecular alterations in UMs is being incorporated with clinical information to develop a prognostic classification of UM.

---

**OP1**

**The effect of chronic preconception paternal alcohol intake on sperm methylation signatures and subsequent gene expression in mouse offspring**

**J Knezovich** (University of the Witwatersrand), A Ferguson-Smith (University of Cambridge), M Ramsay (University of the Witwatersrand and National Health Laboratory Service)

Background Epigenetic mechanisms regulate gene expression, and are particularly important in regulating foetal development. DNA methylation within promoter and regulatory regions influences gene activity. DNA methylation has been shown to be sensitive to the presence of alcohol.

Aim Quantify sperm DNA methylation of male mice chronically exposed to ethanol prior to conception, and examine differential gene expression in sired

offspring (embryos). It was hypothesised that excessive alcohol exposure of male mice prior to conception will alter sperm DNA methylation, which will subsequently be inherited by offspring, consequently eliciting a change gene expression, and manifesting phenotypically as growth retardation.

Methodology Male C57BL/6 mice were chronically exposed to 3g/kg ethanol for 10 weeks. Male mice were mated with untreated females. Sperm DNA was extracted from exposed males. Genome-wide sperm DNA methylation was quantified using RRBS. Organs of day 16.5 embryos (n=164) were harvested, weighed, and total RNA was extracted. Embryonic gene expression levels were quantified in three tissues (placenta, brain and liver) using a genome-wide array.

Results Significantly altered DNA methylation profiles were noted across the sperm epigenome of ethanol-exposed males ($p$<0.05 to $p$<0.0001). Gene expression profiles were significantly altered in all three tissues from embryos sired by ethanol-exposed males. Brain and liver weight was significantly reduced in male embryos of ethanol-exposed sires ($p$<0.05).

Conclusion Chronic preconception paternal alcohol exposure alters sperm DNA methylation in a locus-specific manner, which is associated with aberrant embryonic gene expression across three tissues and a mild growth-restricted phenotype in the embryonic brain and liver.

---

**OP 2**

## Loss- of- function pcsk9 variants associated with sustained reductions in ldl-c levels amongst a black south african population over a 5 year period

**T Chikowore** (Center of Excellence in Nutrition), K Conradie (North-West University), T van Zyl (North-West University)

Loss-of-function variants in the PCSK9 gene have been associated with lifelong reductions of LDL-C levels in numerous longitudinal studies amongst black Americans and no similar investigations had been done in Africa. This study set out to assess the association of the A443T and C679X PCSK9 variants with LDL-C levels amongst black South Africans over a 5 year period. A longitudinal study nested in the PURE STUDY 2005 and 2010 data sets was done amongst 1800 healthy male and female volunteers. LDL-C was estimated using the Friedwald equation. Genotyping of the C679X and A443T PCSK9 variants was done using protocols from Applied Bio systems. Chi-square tests were done to assess for HWE status of the variants. Univariate analyses were done to assess the association of A443T, C679X and a combined count genetic risk score of the variant carriers and their related non-carriers with LDL-C levels. LDL-C levels reductions for carriers of A443T and C679X in 2005 were 12% and 26.6% (p<0.05) respectively; then for 2010 12% and 38% (p<0.05) respectively compared to their related non-carriers. Carriers that carried a total of 2 risk alleles (GRS=2) of the A443T and C679X were associated with a 45% and 46% reduction in LDL-C in 2005 and 2010 respectively (p<0.05) compared to non-carriers in spite of other confounders like age, sex and BMI. The results of this study indicated that the carriers of

A443T and C679X variants have sustained lower LDL-C levels and potentially low CVD risk amongst a black South African population

---

**OP 3**

## Association and interaction of the related types XI and V collagen genes with chronic Achilles tendinopathy in independent populations from South Africa and Australia

**M Collins** (Medical Research Council and University of Cape Town), M Hay (University of Cape Town), A September (University of Cape Town), M Posthumus (University of Cape Town), J Patricios (Morningside Sports Medicine, Johannesburg and University of Pretoria), R Collins (The Centre for Sports Medicine & Orthopaedics, Johannesburg), A Branfield (The Centre for Sports Medicine & Orthopaedics, Johannesburg), J Cook (Monash University, Melbourne, Australia), C Handley (La Trobe University, Melbourne, Australia)

Background: Type XI collagen, which is expressed in developing tendons and is encoded by the *COL11A1*, *COL11A2* and *COL2A1* genes, shares structural and functional homology with type V collagen (coded by *COL5A1* and other genes), which plays an role in collagen fibril assembly. We investigated the association of three polymorphisms in *COL11A1* and *COL11A2* with Achilles tendinopathy (AT) and whether these polymorphisms interact with *COL5A1* to modulate the risk of AT.

Methods: One hundred and eighty-four participants diagnosed with chronic AT (TEN) and 338 appropriately matched asymptomatic controls (CON) were genotyped for the functional *COL11A1* rs3753841 (T/C), *COL11A1* rs1676486 (C/T) and *COL11A2* rs1799907 (T/A) polymorphisms.

Results: Although there were no independent associations with AT, the TCT pseudohaplotype constructed from rs3753841 (T/C), rs1676486 (C/T) and rs1799907 (T/A) was significantly over-represented ($p=0.006$) in the TEN (25.9%) compared with the CON (17.1%) group. The TCT(AGGG) pseudohaplotypes constructed using these type XI collagen polymorphisms and the functional *COL5A1* rs71746744 (-/AGGG) polymorphism were also significantly over-represented ($p<0.001$) in the TEN (25.2%) compared with the CON (9.1%) group.

Discussion: The genes encoding structural and functionally related type XI (*COL11A1* and *COL11A2*) and type V (*COL5A1*) collagens interact with one another to collectively modulate the risk for AT. The TCT(AGGG) pseudohaplotype is believed to be associated with increased types V and XI collagen production. The results of this study provide additional evidence that interindividual variations in collagen fibril assembly might be an important molecular mechanism in the aetiology of chronic AT.

---

**OP 4**

**A Pathway-based Approach to Identify Novel Parkinson's Disease (PD) Genes in the South African Afrikaner Population**

**B Glanzmann** (Stellenbosch University), J Gamieldien (South African Institute for Bioinformatics), G Geldenhuys (Stellenbosch University), J Carr (Stellenbosch University), S Bardien (Stellenbosch University)

Parkinson's disease (PD) is a debilitating neurodegenerative disorder with a significant genetic component. Whole exome sequencing (WES) has been used to identify novel disease-causing genes for PD. In a cohort of PD patients recruited for genetic studies, it was determined that approximately 30% of these individuals were Afrikaner. By using genealogical analyses, WES and bioinformatics approaches, we aimed to identify a novel PD gene in this population.

Genealogical analysis was conducted on recruited Afrikaner PD families with a young age at onset. Exome sequencing was performed using an Illumina Genome Hiseq 2000™, sequences were aligned using NCBI human reference genome 37.2. A customized bioinformatics pipeline was designed to exclude known PD-causing genes and to identify novel disease-causing genes. Pathway analysis was conducted using the open source DAVID software.

Genealogical data revealed that six of the apparently unrelated Afrikaner families were linked to a founder couple and three of the probands were selected for WES. Bioinformatics analysis identified approximately 27 000 overlapping novel variants in 931 genes of which 108 are directly involved in mitochondrial dysfunction, 13 in oxidative stress, 77 in endosome vesicle recycling and 112 in protein aggregation pathways respectively.

The identification of novel PD genes would reveal important insights into the pathobiology of PD, particularly since known genes do not appear to play a significant role in South African patients. Moreover, building a bioinformatics pipeline to manage and annotate variants that have been generated using WES provides exciting new prospects for genetic research in South Africa.

---

## COUNSELLING CONUNDRUMS

*Keynote Presentation:*

**Points of control of genetic testing**

**C Patch** (Guys & St Thomas' NHS Foundation Trust, Kings College London. London United Kingdom)

Policy developments in relation to control of genomic tests, in particular the debate around direct to consumer (DTC) genetic tests may act as a case study for considering the processes for implementation of genomics in health care. Concerns that have been raised in relation to DTC include scientific and

clinical validity of these tests and their clinical utility, the quality of the testing services, unnecessary anxiety/false reassurance, further costs to individual and publicly funded health services (NHS), data protection, loss of public trust and confidence in the science. The proponents of DTC have challenged owner ship of genome and data and made assertions of medical paternalism. Developments in the arena of DTC genetic tests have played out against a background of technological development, which has highlighted the necessity for flexible approaches to regulation, which allow for innovation but provide appropriate protection. Devices regulation both in the USA and Europe has been challenged and the time needed to review and change devices regulation has meant that the technology and new business models have developed faster. Tests are performed to answer a clinical question with the aim of informing management and prognosis. As a clinician we need to establish what the question is that we are trying to answer, is the test of high quality and accurate, what does the result mean and is it useful. Systems of clinical and professional guidelines and assessment by payee such as United Kingdom Genetic Testing Network act both as mechanisms for implementation and also for control. It will be important to keep in mind that the work in genomic testing has already developed agreement in the principles underpinning the clinically targeted application of analyses for the purpose of health care and that there are multiple points of control. This may help meet the challenge of balancing innovation with responsible application.

---

**OP 5**

## Would you terminate a pregnancy affected by Sickle Cell Disease? Differential views of doctors, parents and adult patients in Cameroon (sub-Saharan Africa)

**A Wonkam** (University of Cape Town), A Njamnshi (University of Yaounde), D Mbanya (University of Yaounde), J Ngogang (University of Yaounde), F Angwafo 3rd (University of Yaounde)

Background: Sickle Cell Disease (SCD) is a debilitating illness that affects life expectancy for patients. Cameroon has a population carrier frequency of 8 to 34%. It is possible to test for SCD before birth, to allow reproductive options to parents. However, under Cameroonian Law, medical abortion is permitted '...if it is done by an authorized professional and justified by the need to save the mother from grave health jeopardy…' Fetus pathology like SCD is not considered!

Objectives and Methods: structured quantitative sociological questionnaires survey, of 110 doctors, 130 parents with one living child with SCD, and 89 adults patients suffering from SCD, to study their views regarding prenatal genetic diagnosis and termination of SCD-affected pregnancy.

Results: the majority were urban dwellers and Christian. The majority accepted prenatal genetic diagnosis for SCD (78.7%, 89.8% and 89.2%, respectively). The majority of parents accepted the principle of termination of SCD-affected pregnancy (62.5%), but doctors and adults patients were less comfortable (36.1%, and 40.9 % acceptance, respectively). Parents and patients who rejected termination of pregnancies claimed ethical reasons

(69.1 and 78.1%) while those who found medical abortion acceptable cited fear to have an SCD-affected child (98.1 and 88.9%) and the poor quality of the affected child's health (92.6% and 81.5%). Amongst parents, acceptance of the principle of medical abortions increased with unemployment ($p<.01$) and single marital status ($p<.05$).

Conclusions: Differential views of these major players, regarding medical abortion for SCD in Cameroon, could lead serious ethical conflicts. Policies and practices implications are discussed.

---

**OP 6**

**Inherited breast and ovarian cancer: a review of the available genetic counselling and testing services in Johannesburg**

**M Gomes** (National Health Laboratory Service)

Inherited breast and ovarian cancers account for between 5 to 10% of all breast cancer and 10 to 15% of all ovarian cancer cases. In South Africa, testing for these inherited cancers is limited to those individuals with a high-risk family history of breast/ovarian cancer and those relatives of individuals with identified mutations in the predisposing genes, *BRCA1/2*. This study aimed to assess the genetic counselling service offered to patients in terms of *BRCA1/2* testing and to assess patients' experiences of the genetic counselling service. Information was obtained from the files of 218 patients counselled at the Genetic Counselling Clinics of the Division of Human Genetics, University of the Witwatersrand and National Health Laboratory Service from 2001 to 2010. Results indicated that 82% of counsellees were white and either of Ashkenazi Jewish (45%) or Afrikaner (21%) ancestry. Although 61% of counsellees were as yet unaffected with breast/ovarian cancer, 89% had an affected first degree relative. Genetic testing was offered to 78% of counsellees (uptake of 81%), 90% of which was performed nationally. Fifty counsellees participated in the telephonic questionnaire. The majority of comments were positive; however some respondents raised the issue of a lack of knowledge of the service amongst medical professionals. Overall, the study reflected the current *BRCA* testing available and the need to investigate susceptibility to inherited breast/ ovarian cancer in the black population. Marketing to the general population and other medical professionals may also assist in reaching a broader demographic and more high risk individuals.

---

**OP 7**

**Anxiety, Assurance, Ambiguity…to be or not to be?**

**N Kinsley** (GC Network)

The general expectation of a genetic test result is that it will be deterministic.

The primary use for genetic testing has been to identify risk for rare heritable conditions, which often have a poor prognoses.

Genetic counsellors address concerns and help families adapt to the impact of a genetic condition, often underpinned by an informative and predictive genetic test.

New era 'personalised' genetic testing has emerged and is more accessible. The tests include prenatal and pre-pregnancy screening, testing for risks for common disorders, and behavioural traits. Test results are not necessarily definitive - complicating risk interpretation, leading to increased anxiety, and challenging the genetic counsellor's role.

Two cases are presented evaluating the impact that 'personalised' genetic tests have on genetic services. In one case, testing included a 'fun' test for a behavioural trait and the other, a pre-pregnancy screening assessing reproductive risks. The cases are reviewed and comparisons made, focusing on responses to the results.

The tests were performed internationally and results were emailed to the individuals. In neither case was there pre-test counselling. The responses were similar; feelings of increased anxiety, loss of control, frustration, and shame. A positive outcome was only achieved once predictiveness was increased.

This study highlights the need for further discussion regarding the provision of personalised genetic tests and the role of genetic counsellors as non-directive support for the individual, their family, and the greater community.

---

**OP 8**

## Risk communication in Advanced Maternal Age genetic counselling sessions

**T Wessels** (National Health Laboratory Service and University of the Witwatersrand), C Penn (University of the Witwatersrand)

Providing risk information is central to genetic counselling and is a complex process. Research has concentrated on professional and patient perspectives, leaving the area of how risks are communicated in interactions under-researched.

This paper examined how genetic counsellors communicated risks during a genetic counselling session with women of advanced maternal age in a public health setting. Seventeen sessions were conducted in English by six genetic counsellors. The sessions were video and voice recorded and transcribed verbatim. The data were analysed using principles of conversation analysis, which allows the researcher to analyse the structure and order of the conversation, and how the participants understand and relate to each other. This method involves watching, listening and reading the transcripts several times over which allows patterns to emerge and interpretations to be made.

An analysis of the risk communication revealed that the counsellors provided risks in the form of 1 in (X); percentages; and they provided both negative and positive risks. Providing a risk was accompanied by explanations with the counsellors using appropriate analogies.

The results showed how risks were communicated in interactions. These provided some insight into the complexity of the process, as well as how theories translate into practice. These data, combined with findings from other studies on perceptions and outcomes assist in providing an understanding of the process of genetic counselling. These can be used to improve the process of genetic counselling and ensure that patients are able to appropriately use the risk information to make informed decisions.

---

## TRANSLATION TRENDS

*Keynote Presentation:*

**NextGen thinking for genetics and genomics in Africa**

**A Adeyemo** (Center for Research on Genomics and Global Health, National Genome Research Institute, NIH, Bethesda, Maryland, USA)

Several factors have made this an unprecedented time to conduct top-notch research in genetics and genomics in Africa. These include: new funding initiatives (such as the H3Africa Initiative); the availability of new tools, technologies and approaches for genotyping and sequencing that can better characterize African genomes; advances in our current understanding of genetic diversity and population structure across Africa; and, because of a dearth of previous studies, numerous opportunities to conduct research into a wide variety of diseases and conditions. These exciting developments have led to a renewed interest in the application of the latest tools and technologies to dissecting the genetic architecture of multiple diseases and traits on the continent, as well as in the ethical, legal, and social implications in research and clinical practice. This talk will discuss how these new opportunities should be accompanied by new ways of thinking about doing genetics and genomics in Africa. Study design, genotyping and/or sequencing strategies, analytic approaches, follow up plans and setting up collaborations should all be informed by the most recent advances in the field rather than simply repeating what has been done in the past. In addition, it is essential to account for the unique characteristics of the populations under study and to attempt to exploit the often distinctive clinical epidemiology of the diseases being studied. Coupling “nextgen thinking” with nextgen tools and technologies holds the promise of returning truly novel and impactful findings in genetics and genomics research in Africa.

---

**OP 9**

## Using induced pluripotent stem cells to model neuronal degeneration in Spinocerebellar Ataxia type 7

**L Watson** (University of Cape Town), J Scholefield (Council for Scientific and Industrial Research), R Ballo (University of Cape Town), S Cowley (University of Oxford), D Smith (University of Cape Town), M Weinberg (University of the Witwatersrand), S Kidson (University of Cape Town), J Greenberg (University of Cape Town), M Wood (University of Oxford)

Spinocerebellar ataxia type 7 (SCA7) is a dominantly inherited neurodegenerative disease, resulting from a trinucleotide repeat expansion in the *ataxin-7* gene. The Ataxin-7 protein is known to regulate gene expression through association with histone acetylation complexes, and transcriptional dysregulation, caused by mutant Ataxin-7, is an early marker of disease progression. This study aimed to establish patient-derived induced pluripotent stem cell (iPSC)-based models of SCA7, for the investigation of disease pathogenesis, with particular reference to a transcriptional phenotype.

iPSCs were generated through the transduction of SCA7 patient and control cultured dermal fibroblasts with retroviral vectors carrying four pluripotency genes. These iPSCs were characterised with respect to markers of pluripotency and transgene silencing, before undergoing neuronal differentiation. Markers of disease pathogenesis, including transcriptional dysregulation, were assessed by means of quantitative real-time PCR and immunocytochemistry.

Preliminary results following neuronal differentiation indicate significant changes in the expression of several genes, including two heat shock proteins previously implicated in SCA7 pathology (*DNAJA1* and *HSP27, p*=0.01). Current work focuses on refining the neuronal model, using lineage-specific differentiation protocols to generate cerebellar neurons, and subjecting neurons to *in vitro* models of cellular aging and stress.

The development of these novel cell models for the South African SCA7 patient cohort offers the first opportunity to study the molecular basis of SCA7 in disease-relevant cells from human patients. The identification of a disease-associated phenotype in these cells confirms the central role of transcriptional regulation in SCA7 pathogenesis, which may serve as a valuable marker for disease progression and therapeutic efficacy.

---

**OP 10**

## Whole genome sequencing identifies putative primary congenital glaucoma causal gene in a South African family

**N Carstens** (University of the Witwatersrand), S Williams (University of the Witwatersrand), T Carmichael (University of the Witwatersrand), A Choudhury (University of the Witwatersrand), S Goolam (University of the Witwatersrand), S Hazelhurst (University of the Witwatersrand), M Ramsay (National Health Laboratory Service and University of the Witwatersrand)

Primary congenital glaucoma (PCG) is a prominent cause of juvenile-onset blindness worldwide. PCG most often follows an autosomal recessive inheritance pattern and four genomic regions that harbour PCG causal genes have been identified through linkage analysis. The genes responsible for the linkage signals in GLC3A and GLC3D have been identified as *CYP1B1* and *LTBP2*, respectively, while the genes for GLC3B and GLC3C remain unknown. This study aims to identify the PCG causal variant(s) in a South African family of mixed ancestry in whom two of the five children are affected.

Peripheral blood leukocyte-derived DNA samples from one PCG-affected child and her unaffected non-consanguineous parents were sequenced at an average coverage of 40X by Complete Genomics, using their short-read sequencing-by-ligation technology. A comprehensive set of filters was applied to narrow down a set of putative PCG causal variants.

On average, 98% of each genome had a coverage of at least 10X per base. We identified between 3 934 142 and 3 808 619 single nucleotide variations (SNVs) in the individuals. Systematic filtering using criteria that were optimized to take mode of inheritance, population-level allele frequency and possible biological relevance into account, identified a set of plausible PCG causal variants. These are being validated in the family and runs of homozygosity surrounding one of the candidates suggest that the mutation is identical by descent. In addition, a further eight PCG patients are being screened.

In conclusion, this study validates a whole genome sequencing approach for the identification of disease causing mutations.

---

**OP 11**

## The identification of novel variants associated with antipsychotic treatment response through the use of exome sequencing

**B Drögemöller** (Stellenbosch University), D Niehaus (Stellenbosch University), B Chiliza (Stellenbosch University), L van der Merwe (Stellenbosch University), G Wright (Stellenbosch University), M Daya (Stellenbosch University), E Hoal (Stellenbosch University), L Asmal (Stellenbosch University), R Emsley (Stellenbosch University), L Warnich (Stellenbosch University)

Schizophrenia places an immense socio-economic burden on society and current treatments have substantial limitations. As African populations have

been under-represented in genomic research, this study aimed to identify unique patterns of variation that affect antipsychotic response in the context of South Africa.

A well characterised discovery cohort of South African first episode schizophrenia patients receiving antipsychotic treatment (n=104) was utilised to identify a subset of patients on extreme ends of the treatment response spectrum for exome sequencing (n=11). These exomes were analysed utilising BWA, SAMtools, GATK, SeattleSeqAnnotation, VAAST, PolyPhen and SIFT. Thereafter, the Illumina BeadXpress assay was used to genotype 284 prioritised variants and a further 100 ancestry informative markers in the discovery cohort and a further two replication cohorts (n=480). Statistical analyses were subsequently performed to identify associations with treatment response.

Statistical analyses in the discovery cohort identified significant associations ($P<1.0x10^{-5}$) with six variants, one of which has previously been associated with antipsychotic treatment response. The remaining five variants resulted in amino acid changes that were predicted to alter the protein function of five novel genes. Two of these genes have previously been implicated in susceptibility to other psychiatric disorders, the symptoms of which overlap with schizophrenia.

This study successfully implemented a strategy, which made use of a well-characterised cohort and genomic technologies, the results of which will be tested in the replication cohorts. In so doing, this study was able to identify novel genes that may be involved in antipsychotic treatment outcomes and replicate previous findings.

---

**OP 12**

## Next Generation Sequencing for Retinal Degenerative Disorders; speedbumps on the road to providing a genetic diagnosis.

**L Roberts** (University of Cape Town), S Barton (St. Mary's Hospital, Manchester, UK), G Black (University of Manchester), S Ramsden (St. Mary's Hospital, Manchester, UK), R Ramesar (University of Cape Town), J Greenberg (University of Cape Town)

The vast clinical and genetic heterogeneity displayed by Retinal Degenerative Disorders (RDD) confounds molecular diagnoses of these diseases. Next Generation Sequencing (NGS) has been a growing trend in RDD research as it allows simultaneous screening of many candidate genes.

Samples from 4 South Africans with different RDD were selected for NGS. 105 genes were targeted using Agilent SureSelect Custom design and sequenced on an ABI SOLID 550XL system. Clinically significant variants were verified by Sanger sequencing, and known polymorphisms were removed from the data prior to reporting. The technical reports listed 9 - 24 unconfirmed variants of unknown clinical significance per sample.

Two patients had mutations in genes that were not consistent with their diagnosis of Stargardt disease (STGD). Mutations in KCNV2 cause cone dystrophy with a specific electroretinogram pattern, while mutations in *OTX2*

cause microphthalmia and early-onset RDD with pituitary dysfunction.

One patient had a homozygous mutation in *RPE65,* confirming the diagnosis of possible Leber congenital amaurosis (LCA).

One patient with type II Usher syndrome had a homozygous mutation in the *MYO7A* gene, which causes the more severe type I Usher syndrome.

Both the patients with suspected STGD should be clinically re-examined to ascertain whether their phenotype is consistent with the genotype. Inconsistencies would further underscore the heterogeneity of RDD and suggest that candidate-free screening should be considered in future. Importantly, the patients with LCA and Usher syndrome could benefit from current gene therapy trials specifically for these two genes.

---

## DELVING INTO DELIVERY

*Keynote Presentation:*

**Attaining human dignity for people with birth defects**

**AL Christianson** (Division of Human Genetics, National Health Laboratory Service & University of the Witwatersrand, Johannesburg, South Africa)

For millennia people with birth defects have been stigmatised, marginalised, and discriminated against, diminishing their human dignity and abrogating their human rights. Isidore Geoffroy Saint Hilaire and Charles Darwin began the process of achieving human dignity for people with birth defects in the middle of the 19th century. The United Nations' Universal Declaration of Human Rights, promulgated in 1947, defined the circumstances for achieving human dignity in health care for people with birth defects. This was achieved over the next 65 years through the insight, hard work and dedication of a select group of people and organisations. This paper reviews the history of people with birth defects culminating in the World Health Organisation's 2010 World Health Assembly resolution WHA 63.17 which prioritised services for the care and prevention of birth defects, particularly in middle- and low-income nations. It is considered that this resolution achieved human dignity in health care for people with birth defects. The endeavour to translate this achievement into human rights in health care for people with birth defects is the next objective.

---

**OP 13**

**National Birth Defects Data: 2006-2012**

**V Mtyongwe** (National Department of Health), D Tshikedi (National Department of Health), K Sivnannan (National Department of Health), C Aldous (University of Kwa-Zulu Natal)

The Birth Defects Notification tool (data collection tool) was introduced nationally by the National Department of Health (NDoH) in 2006 to standardise birth defects notification. It was required that all birth defects be reported to provincial Departments of Health and then forwarded to the Sub-directorate Human Genetics at the NDoH. This initiative has grown since its implementation and we are now able to reflect on the data collected. The dataset forms a valuable foundation for a way forward in birth defects surveillance albeit we recognise its shortcomings.

Birth defects notifications provided by all provinces from July 2006 to December 2012 were analysed critically. These notifications were received by fax, post or courier. On receipt, data was captured at the Sub-directorate in a database using Microsoft Access, exported into Microsoft Excel and

descriptive statistics performed. Statistics for the scope of the birth defects and reporting compliance were gleaned.

Since the implementation of the tool, 12 180 birth defects have been reported across the country. There have been discrepancies regarding reporting leading to under-reporting of birth defects, as well as compliance in completing the notification tool.

Whilst the current Birth Defects Notification tool provides some valuable data, getting a comprehensive picture of true birth defects incidence is not being delivered. However, we believe that building on this data reporting foundation together with increased training in the provinces, will lead to an improvement in the reporting compliance and forwarding of birth defects notifications to the NDoH.

---

**OP 14**

**A comparison of genetics services specified in Policy Guidelines issued by the DoH in South Africa in 2001 and the Tertiary Definitions of 2013 and an evaluation of progress made to date.**

**H Malherbe** (University of Kwa-Zulu Natal), C Aldous (University of Kwa-Zulu Natal)

We evaluated the development of genetics services since the publication of the Human Genetics Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities in 2001. The 20th March 2013 Policy Guideline: Tertiary Services Definitions, the product of a national initiative to develop a National Tertiary Services Plan, provides an opportunity to evaluate progress and consider an approach to implement these recommendations.

The 2001 Guidelines recommended over 400 medical scientists and technologists' service the country, although fewer than 50 were employed at the time. In 2012, Kromberg *et al* reported only 11 HPCSA registered medical geneticists, which is far from the recommended criteria in the 2001 Guidelines requiring two full-time clinical geneticists per 1,000,000 of the population. The 2013 Policy Guideline defines genetics service at the tertiary level, which will require specialist service.

The prevalence of serious congenital disorders estimated as 53.4 per 1000 live births (Christianson *et al,* 2006) was found to be 3.6 per 1000 live births based on birth defect notifications collated nationally, and totalled 7007 for the two year period 2010-2012 (Vuyisiwa Mtyongwe, DoH, Pers. Comm). This suggests only a small percentage (6.68%) of birth defects are being recorded. This indicates issues to be addressed in the process of documenting and collating these data, as current efforts do not meet requirements.

The renewed government commitment to genetics services through the publication of the 2013 Policy Guidelines provides an opportunity to take a new approach to implementing and realising these national goals.

---

**OP 15**

**Genetic Services and Genetic Testing in South Africa.**

**JGR Kromberg** (National Health Laboratory Service and University of the Witwatersrand), AL Christianson (National Health Laboratory Service and University of the Witwatersrand)

South Africa has had genetic services available in the two major centres for about four decades and in the smaller centres for a shorter period.

Objectives: these were to investigate the nature of these services, including the genetic testing facilities, and the context in which they are offered.

Methods: demographic data were collected from local available statistics. Then key human geneticists in the major centres were approached for data, initially for the year 2008, regarding their clinical and laboratory services, their training and research programmes, and their support from local, provincial and national authorities. These data were collated and analysed to give the results.

Results: the local services are small, well organised and based in academic centres, with limited funding from provincial and national health services (specifically the National Health Laboratory Service). Genetic counselling services (eg. 7313 cases seen in 2008) and laboratory testing (eg. 16073 genetic tests performed in 2008) are provided in four academic departments. These services are used by local patients, as well as some from neighbouring countries. Training of scientists, genetic counsellors and medical geneticists is available, but internships and jobs are few and vacated posts are frozen. Research relevant to the local populations is undertaken. Less than one tenth of the required staff, according to the WHO guidelines, is available to provide services.

Conclusion: South Africa has the capacity to provide reputable and appropriate genetic services, comparable to those offered elsewhere, but the lack of political will and commitment, funding and employment opportunities, from National and Provincial Departments of Health and the National Health Laboratory Service, is leading to the deterioration of the service.

---

## CLINICAL CONVERSATIONS

*Keynote Presentation:*

**Cancer genetics: linking laboratory and clinical advances**

**A Lucassen** (University of Southampton, United Kingdom)

The last decade has seen tremendous advances in our understanding of the inherited components of cancer. A concomitant rapid decrease in the cost- and increase in the speed- of genetic testing means that the cancer geneticist has many more laboratory tests to offer patients who enquire about their

cancer risks. Yet the interpretation of molecular findings can still be very dependent on interpretation of a family history, or of the characteristics of diagnoses, or results of investigations in a relative. The art of cancer genetics is likely to require the assessment of a family history for some time yet. This talk will review some of these developments and distinguish between multifactorial and highly penetrant components of cancer predisposition, so that patients can be fully cognisant of the clinical utility of any test they might decide to have.

---

**OP 16**

**Genetic testing for haemoglobinopathies in Johannesburg, south Africa: a thirty-year review**

**A Krause** (University of the Witwatersrand), T Wainstein (University of the Witwatersrand), F Essop (National Health Laboratory Service and University of the Witwatersrand), Q Goodyear (National Health Laboratory Service)

Haemoglobinopathies are common monogenic disorders, seen mostly in regions where malaria occurred. Population migration has resulted in individuals with haemoglobinopathies being identified in many countries globally. Further, the first molecular genetics services for diagnostic testing and prenatal diagnosis were established, worldwide and in South Africa, for haemoglobinopathies.

This study aimed to analyse the diagnostic service offered by the Division of Human Genetics, NHLS/WITS from 1983-2012.

A retrospective file analysis was performed for all individuals who had molecular genetic testing for alpha-thalassaemia, beta-thalassaemia and sickle cell anaemia, to examine indications for testing, population origins of patients and molecular genetics findings.

Alpha-thalassaemia testing was performed predominantly to explain microcytic hypochromic haematological indices. Five common alpha-globin deletions have been identified, the most common being the $-\alpha^{3.7}$ in individuals from many different ethnic groups.

For beta-thalassaemia and sickle cell anaemia most testing was performed as part of prenatal diagnostic workup. For sickle cell anaemia, 112 prenatal tests were performed for 77 families, mostly of African origin. For beta-thalassaemia, 59 prenatal tests were performed for 43 families. Families with beta-thalassaemia were mostly of Indian or Mediterranean origin. The commonest mutation identified in all Indian groups was c.92+5G>C, accounting for 41% of mutations in Muslims and 58% in Hindus. In individuals from the Mediterranean, c.93-15T>G was the commonest mutation (77%).

The molecular genetics service offered to individuals in South Africa with haemoglobinopathies has improved technically and developed a knowledge base, so that it provides a comprehensive service specific to the needs of the local populations.

---

**OP 17**

## Evaluation of a programme for Disorders of Sex Development (DSDs) management in Cameroon: What have we learnt?

**W Joko** (University of Yaounde), F Mouafo (University of Yaounde), S Dahoun (University Hospitals of Geneva), P Mure (Centre Hospitalier Universitaire de Lyon, France), C LeCoultre (University Hospitals of Geneva), A Wonkam (University of Cape Town)

Background:

In 2009 a project was launched to diagnose and manage children with anomalies of the external genitalia including patients with DSDs. This was done with collaboration of the Ministry of Public Health and a Swiss charity organization.

Objective:

1. To determine the different aetiologies of DSDs in our Cameroonian population
2. To describe the genetic diagnosis
3. To describe the management challenges
4. To address ethico-legal and social issues (ELSI).

Methods:

1. Biannual multidisciplinary consultations with local and international professionals
2. Cytogenetic and molecular genetics analyses (locally and abroad)
3. Medical and local surgical management
4. Regular patient follow-up by local and international teams

Results:

265 patients were consulted; 175 were diagnosed with external and internal genitalia anomalies:

1. Hypospadias 90 cases (51.4%): 7 anterior, 41 middle and 42 posterior
2. 46, XX DSD, 41 cases (23.4%): CAH (12); 46, XX ovotesticular DSD SRY negative (14); Gonadal dysgenesis (2), Mullerian abnormalities (8); cloacal extrophies (5).
3. 46, XY DSD 29 cases (16.6%): Disorders of androgen synthesis or action (14); 46, XY gonadal dysgenesis (4); Kallmann' syndrome (3), 46,XY CAH (1), 46,XY cloacal exstrophy (7)
4. Sex chromosome DSD 15 cases (8.6%): Turner's syndrome (13), Klinefelter's syndrome (2).
5. 9 have been operated, 7 with CAH. 2 patients with CAH have had legal gender reassignment.

Conclusion:

The increasing number of patients diagnosed with DSDs reveals the necessity to build local technical and human resources to face the multiple management challenges. ELSI aspects specific to our sub-Saharan African context must be further explored.

**OP 18**

## Mitochondrial disorders in South African patients: a next generation sequencing approach to unravel the aetiology

**F van der Westhuizen** (North-West University), E Schoeman (North-West University), M Schoonen (North-West University), J Elson (Newcastle University), R Louw (North-West University), I Smuts (University of Pretoria)

Mitochondrial disorders (MDs) are the most prevalent inherited metabolic disease group and result from deficiencies in the mitochondrial oxidative phosphorylation system. Genetic data to unravel the aetiology of MDs in African populations have been lacking and diagnostic and management protocols currently in use are mostly based on non-African populations. With more than 100 genes on either mtDNA or nDNA already known to be involved, molecular diagnostics are faced with a daunting task. We used next generation DNA sequencing technology to investigate the involvement of mtDNA variants in a South African cohort of patients.

Next generation sequencing technology was used to sequence the complete 16.5 kb muscle mtDNA of 103 patients diagnosed with a muscle respiratory chain deficiency. The average base coverage was 143 and patient sequences were compared to the reference sequence for human mtDNA. After assigning haplogroups using Phylotree, a selection of web-based databases and data mining tools were used for further analysis of mtDNA variants.

In this cohort, where 68% were assigned to (African) macro-halpogroup L, it was confirmed that the number of substitutions was significantly higher in African patients with numerous novel variants with pathogenic potential. Strikingly, with one exception no commonly reported syndrome-associated mutations were found.

These results support clinical observations in this cohort where a lack of syndromic phenotypes was observed. It further indicates that current mutation screening approaches are limited at best and that population-specific investigations in addition to pathogenicity evaluations are required to better resolve the aetiology of this complex disease in Africa.

---

**OP 19**

## New evidence on the epidemiology of fetal alcohol syndrome in South Africa.

**M Urban** (Stellenbosch University), L Olivier (Foundation for Alcohol Related Research), D Viljoen (Foundation for Alcohol Related Research), M Temmerman (University of Ghe), M Chersich (University of Witwatersrand)

### Introduction:

Fetal alcohol syndrome (FAS), and the fetal alcohol spectrum disorder more broadly, is known to be a considerable public health problem in South Africa, and prevalence has been well characterized in specific communities in the

Western and Northern Cape provinces. However, the dimensions of the problem remain uncertain regarding its geographical and ethnic distribution as well as regarding changes in prevalence over time.

**Methods:**

Review of existing published and unpublished evidence (Witzenberg subdistrict, Western Cape; Kimberly, Northern Cape) on the prevalence of FAS. All studies included were school surveys with the same or similar methodology: a tiered diagnostic approach including anthropometric screening of all children; and dysmorphology examination, neurodevelopmental assessment and maternal/collateral interview for selected children.

**Results:**

The prevalence of FAS varies from 19 per 1000 in communities in Gauteng to 100 per 1000 in De Aar, (Northern Cape) and Aurora, an isolated village in the Western Cape. There is a trend across studies for higher prevalence in more rural and isolated communities, though more recent data from Witzenberg district show a higher rate in the urban poor. High FAS rates were found in black Africans in De Aar and Kimberley (both Northern Cape).

**Discussion:**

FAS is prevalent in most South African communities studied and is not limited to viticulture areas. Contrary to popular perceptions, FAS is not limited to the mixed ancestry community and should rather be considered a South African problem. Findings in Witzenberg may reflect movements of workers off farms and into urban informal settlements.

---

## AFRICAN AVENUES

*Keynote Presentation:*

### Genomic variation in southern African San and Khoe groups

**M Jakobsson** (Evolutionary Biology Centre, Uppsala University, Sweden)

The San and Khoe people currently represent remnant groups of a much larger and widely distributed population of hunter gatherers and pastoralists who had exclusive occupation of southern Africa before the arrival of Bantu-speaking groups in the past 1,200 years and sea-borne immigrants within the last 350 years. Previous mitochondrial DNA, Y-chromosome and autosomal studies have revealed that the Khoe and San harbour some of the most divergent lineages found in living peoples throughout the world. Based on the recent investigations of genome-wide variants, I outline the latest results on the population history of the Khoe and San groups, their relationship and recent admixture to other southern African groups. We found a clear geographic structuring among Khoe and San groups, where the greatest genetic differentiation follows a north to south axis. We also found evidence of an ancestry component tracing to east African groups in a Khoe group,

possibly related to the introduction of pastoralism to southern Africa. We further searched the genome for evidence of adaptation in the immune system due to selective pressure from infectious diseases and found more abundant signatures in the southern Khoe and San groups in contrast to northern groups. We speculate that this observation could be explained by southern groups increased exposure to unfamiliar diseases from greater levels of contact with immigrant groups. Further genomic research on African groups will help bridge the gap that exists in current biomedical resources.

---

**OP 20**

**The introduction of pastoralism practices to southern Africa**

**C Schlebusch** (Uppsala University), G Breton (Uppsala University and École Normale Superieure de Lyon, France), H Soodyall (University of the Witwatersrand), M Jakobsson (Uppsala University)

The spread of farming practices has had a marked influence on how humans are distributed around the globe today. The expansion of Bantu-speaking farmers from west Africa to the whole of sub-Saharan Africa is arguably one of the largest expansion waves of farmers. The expansion of Bantu-speakers into southern Africa was however preceded by the herding culture of the Khoe people, who arrived earlier in a separate expansion event. It is thought that the Khoe culture/people moved from east Africa to southern Africa but whether this event was due to the movement of the pastoralist culture only or of peoples as well, is poorly examined at the moment. This study investigated the first wave of farming to southern Africa associated with the Khoe culture by analyzing both gene based and genome-wide variants in the Nama Khoe pastoralists, in conjunction with extensive African and global comparative data. The data was used to infer to what extent this introduction wave was accompanied by migrating people, where these people originated from and which routes were followed. Through this study the history of the Khoe people have been clarified and placed into a global context of population diffusion.

---

**OP 21**

**Genetic diversity in black South Africans from Soweto**

**A May** (National Health Laboratory Service and University of the Witwatersrand), S Hazelhurst (University of the Witwatersrand), Y Li[3], S Norris (University of the Witwatersrand), N Govind (University of the Witwatersrand), M Tikly (University of the Witwatersrand), C Hon (Novartis Institutes for Biomedical Research), K Johnson (Novartis Institutes for Biomedical Research), N Hartmann (Novartis Institutes for Biomedical Research), F Staedtler (Novartis Institutes for Biomedical Research), M Ramsay (National Health Laboratory Service and University of the Witwatersrand)

Due to the unparalleled genetic diversity of its peoples, Africa is attracting growing research attention. Several African populations have been assessed in global initiatives such as the International HapMap and 1000 Genomes

Projects. Notably excluded, however, is the southern Africa region, which is inhabited predominantly by southeastern Bantu-speakers, suffering under the dual burden of infectious and non-communicable diseases. Limited reference data for these individuals hampers medical research and prevents thorough understanding of the underlying population substructure. Here, we present the most detailed exploration, to date, of genetic diversity in 94 unrelated southeastern Bantu-speaking South Africans, resident in urban Soweto (Johannesburg). Participants were typed for ~4.3 million SNPs using the Illumina Omni5 beadchip. PCA and ADMIXTURE plots were used to compare the observed variation with that seen in selected populations worldwide. Results indicated that Sowetans, and other southeastern Bantu-speakers, are a clearly distinct group from other African populations previously investigated, reflecting a unique genetic history with small, but significant contributions from diverse sources. To assess the suitability of our sample as representative of Sowetans, we compared our results to participants in a larger rheumatoid arthritis case-control study. The control group showed good clustering with our sample, but among the cases were individuals who demonstrated notable admixture. Sowetan population structure appears unique compared to other black Africans, and may have clinical implications. Our data represent a suitable reference set for southeastern Bantu-speakers, on par with a HapMap type reference population, and constitute a prelude to the Southern African Human Genome Programme.

---

**OP 22**

## Common population-specific SNPs identified by mining 1000 Genomes sequence data

**A Choudhury** (University of the Witwatersrand), A Meintjes (Clinical Laboratory Sciences), S Hazelhurst (University of the Witwatersrand), M Ramsay (University of the Witwatersrand and National Health Laboratory Service), J Gamieldien (Medical Research Council), N Tiffin (Medical Research Council), S Aron (University of the Witwatersrand), N Mulder (University of Cape Town), M Jalali (South African National Bioinformatics Institute), O Achinike-Oduaran (University of the Witwatersrand)

Numerous novel common variants have been found to be restricted to individual populations. Comprehensive analysis of these variants is likely to provide important clues to the relationship between genome diversity and adaptation to distinct geographic and environmental conditions.

By mining the most recent 1000 Genomes dataset, consisting of sequence data for 1092 individuals from 14 different populations, we have identified common (MAF>0.05) SNPs, which are unique to each population. A window scan based approach was employed to study the genomic distribution of these common population specific SNPs (CPS-SNPs) and the extent of positive selection in genomic regions enriched with CPS-SNPs. The CPS-SNP enriched regions were also scanned for recombination hotspots and coldspots.

The highest number of population specific common SNPs and structural variants was observed in the two African populations, (the LWK and YRI)

followed by Asian and European populations. We identified many genomic regions that are enriched in CPS-SNPs. Interestingly, distribution of these CPS-SNP enriched regions was also found to be highly population specific. The longest block of CPS-SNP enriched windows for LWK, YRI, Chinese, and JPT were found in/near the PAWR SLCO1B1, RIF1 and MNTR1A genes respectively. Although scans for signatures of selection failed to detect any evidence for a selection bias in these regions, recombination hotspots were found to be very significantly enriched and coldspots significantly depleted from these regions in all the populations studied. This distribution of recombination hotspots/coldspots in the CPS-SNP enriched regions hints at probable mechanisms by which such regions might originate.

---

# WEDNESDAY, 9 OCTOBER 2013

## GO! GENETWORKING: CONCURRENT NETWORKING SESSIONS

### Network session 1: Stem Cells

Panelists: Dr R Bello (CHAIR) (University of Cape Town), Dr L Watson (University of Cape Town) & Prof S Kidson (University of Cape Town)

**OP 23**

**Mesenchymal stem cells – adult stem cells with potentially wide therapeutic applications**

MS Pepper (University of Pretoria), M Potgieter (University of Pretoria), M Alessandrini (University of Pretoria)

Mesenchymal stem cells are abundant in adult tissues, and as their name suggests, can give rise to several tissues of mesodermal origin including bone, cartilage, muscle and adipose tissue. These cells are defined phenotypically by the positive and negative expression of a panel of cell surface markers, and also by their ability to differentiate in vitro into the lineages mentioned above in response to appropriate environmental cues.

This presentation will examine the isolation and characterization of mesenchymal stem cells, their tissues of origin as well as the spectrum of diseases for which their efficacy is being assessed globally in registered clinical trials. An analysis of the clinicaltrials.gov website indicates that > 250 clinical trials covering almost all organ systems and a wide variety of diseases are currently underway. As a reflection of their lack of immunogenicity and immunosuppressive properties, it is noteworthy that the use of autologous and allogeneic cells is roughly equal in these trials. The importance of clinical trials, their registration with the Medicines Control Council, and the requirement for ethics and peer review will also be discussed, as will the importance of patients not having to pay for treatments that are unproven/experimental in nature.

---

**OP 26**

**Engineering cellular models of disease: Genetic surgery on stem cells.**

**J Scholefield** (Council for Scientific and Industrial Research)

Last year Shinya Yamanaka was co-awarded the Nobel Prize in Physiology and Medicine for developing a method to reprogram a terminally differentiated cell into a pluripotent state. These induced pluripotent stem cells (iPSCs) have enormous potential impact in the field of regenerative medicine. However, they have also become a valuable resource in developing genetically accurate models of disease in a dish. This is particularly relevant in aiding our

understanding of how our host genetics lends susceptibility or even resistance to pathogens. Conversely, the ability to remove the variable 'background' of host genetics would be of great value in understanding the pathogenic contribution of a single point mutation, for example. Researchers have recently demonstrated the ability to edit the genome of iPSCs using endonucleases. Thus we can create isogenic cell lines, which are distinguishable only by the discrete and deliberate genetic changes introduced. Understanding how we can engineer such cells and the subsequent applications is thus of great importance.

---

**Differentiation of induced pluripotent stems cells – a focus on retinal degeneration.**

**DC Smith** (University of Cape Town)

Since the discovery of induced pluripotent stem cell (iPSC) technology in 2006, many research efforts have focussed on exploiting the pluripotent nature of iPSCs to derive the cell types of interest for research or therapy. Within the UCT Stem Cell Research Initiative, differentiation protocols have been directed toward studying the cell types affected in the neurodegenerative disease Spinocerebellar ataxia type 7. Various protocols have been successfully utilized to derive neuronal precursors, neurons, photoreceptors and retinal pigment epithelial cells, with many valuable lessons learnt concerning the efficient differentiation and characterization of these cells.

---

**OP 29**

**Fibroblast-derived extracellular matrix directs human embryonic stem cells towards endodermal cell differentiation through an early stage meso-endodermal phenotype**

K Dzobo (International Centre for Genetic Engineering and Biotechnology (ICGEB))

The effect of the insoluble fd-ECM on hESC proliferation and differentiation has not yet been investigated, despite the fundamental insights that such a study may reveal. Cell-derived ECM provides an opportunity not only for physical support but also for the controlled presentation of appropriate biological cues. Here we show that a lung-specific ECM, derived from WI38 cell line, enhances the differentiation of hESCs towards the endoderm lineage. This differentiation occurs through an intermediate stage where there are both endodermal and mesodermal cell lineages within the cell population. In our study, hESCs differentiation was inferred from a strong downregulation in the expression of the stemness markers with concomitant enhanced expression of the endodermal and mesodermal markers. This initial differentiation towards these two lineages suggests either the co-existence of diverse populations of cells of different germ layers or co-expression of markers of more than one lineage in the same hESCs.

The novel findings in this study are that the fd-ECM initially directs hESCs differentiation towards the meso-endodermal lineage, but if hESCs are cultured for a longer time on fd-ECM they eventually assume the endodermal lineage. We also found that integrins such as integrin beta 1 (ITGβ1), ITGα2, and ITGα3 are crucial components of this differentiation process. Matrix or fd-ECM enhanced directed hESCs differentiation not only tries to emulate the embryonic development but also allows accelerated hESCs differentiation on ECM proteins and these proteins are frequently critical components of tissue-engineered grafts. To that end, our results that show fd-ECM induced integrin upregulation in hESCs may propose the design of skin or tissue grafts scaffolds containing ECM proteins in their natural states and inclusion of embryonic stem cells.

---

**OP 32**

## Some proposed guidelines for an ethical approach to stem cell research in South Africa

**J Greenberg** (University of Cape Town), D Smith (University of Cape Town)

The use of patient-derived induced pluripotent stem cells (iPSCs) for *in vitro* disease modelling and testing of potential therapies is a new and exciting prospect that could not have been imagined possible ten years ago. In many instances this approach is now considered being preferable to that of the traditional method of looking at effects in transgenic mice or immortalized cell lines. iPSCs have already been utilised as disease-in-a-dish models to investigate the cellular phenotypes of various genetic disorders, including Parkinson's disease and Down syndrome.

Now that iPSC research is no longer a foreign technology in South Africa there is a need to consider accessing and archiving this type of permanent biological resource for patients with genetic conditions on the African continent.

Given the seemingly endless possibilities for future iPSC-based research, the challenges associated with obtaining comprehensive informed consent from research participants need to be addressed. The scientific community has a responsibility to ensure that research is always based on non-maleficence and that immediate beneficence is not necessarily the prime objective. The fact that the informed consent processes for genomic research in African populations has recently been brought under scrutiny, has highlighted the need to carefully consider these processes and ensure that the consent forms are written in a language that is simple and clearly understandable to participants.

Guidelines for an ethical approach to obtaining comprehensive informed consent for the collection of biological material in order to be able to generate iPSCs for prospective research purposes are now essential.

---

## Networking session 2: Pharmacogenetics

Panelists: Prof C Dandara (CHAIR) (University of Cape Town), Prof L Warnich (Stellenbosch University), Dr G Wright (University of the Western Cape), Dr N Tiffin (University of the Western Cape) & Prof M Ramsay (University of the Witwatersrand & National Health Laboratory Service)

**OP 24**

### Translation of Pharmacogenomics data: where are we in Africa?

**C Dandara** (University of Cape Town)

Pharmacogenomics research is growing in leaps and bounds in Africa, starting as replication studies for observations elsewhere to the current period of targeted sequencing. The discipline investigates differences either in response to treatment or in side effects of therapy that can be explained by genetic variation. Early studies provided a landscape of the distribution of genetic variants with pharmacogenetic relevance. African-specific pharmacogenetic variants were mapped although they only constituted a fraction of the missing heritability. Recent studies have begun to bring the recognition of these differences to the level of clinical practice especially in the field of HIV research. Most of the antiretroviral drugs in use are substrates of drug metabolising enzymes (DMEs) whose genes form the basis of pharmacogenetics. For example, efavirenz (EFV), used in treating pediatric human immunodeficiency virus infection, has central nervous system side effects. A 5-year-old girl with perinatally acquired HIV infection, presenting with new onset absence seizures after starting treatment with EFV was observed to be homozygous for the CYP2B6 516T/T genotype, which is associated with poor EFV clearance. Seizures abated after EFV discontinuation. Predictive values for additional CYP2B6 variants with respect to EFV levels above the therapeutic index have been worked out in the South African context. What is the next step? Up take! In addition to HIV pharmacogenetics, more pharmacogenomics based work in on going especially in schizophrenia, hypertension, inflammatory bowel disease (IBD) warfarin dosing. This presentation will highlight success stories and propose action to speed translation of pharmacogenomics findings.

---

**OP 27**

## Genetic variability of the multidrug and toxin extrusion 1 (MATE1) gene within the Xhosa population of South Africa

C Jacobs (University of the Western Cape), M du Plessis (University of the Western Cape), N Hoosain (University of the Western Cape), B Pearce (University of the Western Cape), **M Benjeddou** (University of the Western Cape)

Solute carrier transporters (SLCs) are membrane-associated transporters that facilitate the passage of solutes, including peptides, bile acids, amino acids, ions, xenobiotics, drugs, and other biologically active compounds, across cell membranes in epithelial tissues, such as intestine and liver. In the intestine, SLCs are critically involved in drug absorption, thus determining distribution and pharmacokinetic characteristics of many drugs. Recent studies suggest that inter-patient variability in response to the antidiabetic drug metformin could be related to polymorphisms in the organic cation transporter (OCT) genes and/or the multidrug and toxin extrusion (MATE) genes. Metformin is also an exceptional substrate for MATE1 and MATE2-K and these proteins play a role in the elimination of metformin into the bile (MATE1). The aim of this study was, therefore, to investigate the genetic variability of the MATE1 gene and to deduce its possible pharmacogenetic implications within the Xhosa population.

Genetic variations of 10 non-synonymous single nucleotide polymorphisms within the SLC47A1 encoding MATE1 were investigated in the Xhosa population. The SNP variants were selected using the SIFT (Sorting Intolerant From Tolerant) program. SIFT was used to predict whether the evaluated SNP polymorphism will likely to cause a functionally neutral or deleterious amino acid change. The SIFT scores were used to prioritize substitutions for further studies. Biological samples in the form of buccal swabs were collected from 150 unrelated voluntary donors from the Xhosa population and residing in the Cape Metropolitan area. One SNaPshot® Multiplex System was specifically designed for the study, successfully optimized and used for genotyping. Hundred genetic profiles were then generated for the 10 SNP variants for the population.

Population genetics data obtained for the investigated SNPs were analyzed using various statistical analysis software. Important population genetic parameters were calculated, and possible pharmacogenetic implications were then discussed. Among others, allelic and genotypic frequencies, as well as linkage disequilibrium were determined and compared with world populations. No significant Linkage Disequilibrium between the investigated SNPs was observed in both populations.

Genomic diversity within sub-Saharan Africa, and for that matter the entire African continent, is relatively under-studied, despite being home to significant portion of human genomic diversity. This study will therefore contribute in bridging the gap in the current knowledge of pharmacogenetic variability in these important populations.

---

**OP 30**

**Defining the need for pharmacogenetic profiling in Africa: A perspective on cytochrome P450.**

**M Alessandrini** (University of Pretoria), M Pepper (University of Pretoria)

African populations are subjected to an increasing burden of communicable and non-communicable diseases, including cardiovascular disorders in the latter. Although the continent accounts for 14.5% of the global population, it carries nearly 30% of the global disease burden. The costs incurred through adverse drug reactions and non-responsiveness to therapy further aggravates the situation, and application of pharmacogenetics principles may afford partial relief. The CYP450 family of enzymes is involved in the oxidative metabolism of many therapeutic drugs. These enzymes are highly polymorphic and account for up to 30% of inter-individual differences seen in a variety of drug responses. CYP450 variability is well documented in Caucasian and Oriental populations, while limited data exists in African populations.

Our objective was to undertake and exhaustive evaluation of CYP450 reports in African populations and in so doing to map out areas of need in the pharmacogenetic field on the African continent. A comprehensive review of the literature was undertaken and a database of all CYP450 reports in African populations was established. An in-depth analysis of genetic variability and the distribution of reports was performed.

The data confirms a paucity of CYP450 reports on the continent and illustrates large regions for where no population information exists. Even where there are reports, little in terms of significance is offered due to the small sample sizes. There is a dire need to address the health problems of Africa, and wide-scale pharmacogenetic profiling of these populations will add significantly to improving patient care on the continent.

---

**Networking session 3: Making Sense of Sequencing**

Panelists: Prof S Bardien (CHAIR) (University of Stellenbosch), Mr H Ganesan (Inqaba Biotechnical Industries), Prof A Wonkam (University of Cape Town) & Dr A Adeyemo (National Institute of Health, USA)

**OP 25**

**Yes – I say to the question: “Does South African have what it takes?**

**C Van Heerden** (Central Analytical Facility (CAF))

Recently Stellenbosch University became the first African institution to sequence a human genome. Fittingly, the work was done for a student from UCT.

The result of the first run was by no means perfect. The run was a mate pair library targeting 1kb inserts sequenced with 60/60bp reads on 6 lanes. The single slide on the 5500xl produced 771,967,755 fragments, with 82% of the reads mapping. The average read length was 56bp (for both tags) and the average base QV of 38 (median of 41). The average cover is 22x. The cost of this run was R39,500 excl. VAT. The cost of the run was in part sponsored by Life Technologies.

Whole genome sequencing is technically “easy”, but there are logistical and financial challenges. These challenges can be addressed and sequencing human genomes in South Africa is now a reality. What are these challenges, how lasting are the solutions and can this be continued into the future? Why is it important that we use South African facilities? These are all valid questions that should be considered and answered.

---

**OP 28**

**Next-generation Sequencing Bioinformatics: “Local is lekker”**

**I Van Jaarsveld** (Centre for Proteomic and Genomic Research (CPGR))

Next Generation Sequencing (NGS) data holds little value without the ability to validate, analyse and interpret the data. This is the realm of bioinformatics: extracting the signal from the noise and inferring functional possibilities. Here we consider the applications and limitations of NGS data in a South African context. Typical analysis workflows are discussed, along with the many challenges one faces during execution. Amongst others, workflow validation and data-lineage auditing standards proposed to support the translation of NGS data into clinically relevant applications are little known and unfortunately underutilised. The computational requirements for data transfer, analysis, and storage are extensive for NGS projects and, apart from posing a significant practical challenge, can inflate the cost of research. How best does one go about analysing whole genome sequencing (WGS) data given South Africa’s resource and skill constraints? The Centre for Proteomic and Genomic Research ran a WGS pilot study on malignant oesophageal tissue from four South African individuals infected with human papilloma virus (HPV) to explore real challenges and practical solutions for NGS bioinformatics in South Africa. Employing a network of local resources, we aim to bolster local capacity and help shift South African research towards more effective utilisation of powerful NGS applications.

---

**OP 31**

**Transforming sequence to product**

**A Olckers** (DNAbiotec®, Pretoria, South Africa)

Taking research results back to the patient (the market) as a product is complex and requires purposeful intervention at many levels. At the minimum the transformation from sequence to product involves:

i. Transformation of the discovery to an invention.

ii. Continued transformation from the invention to an innovation, thus to a product that is traded in the market.

This transformation generally flows via the traditional elements of innovation, which are:

a. Idea.

b. Research.

c. Development.

d. Productisation.

e. Manufacturing.

f. Commercialisation.

The sequence is generated during the research phase and only traded in the market as a product in the commercialisation phase. During the transformation of sequence to product, aspects such as ownership of the sequence, informed consent, data security, validity (both analytical and clinical), clinical utility, legislative vacuums, and intellectual property (IP) rights need to be addressed. These aspects are central to the ethical productisation and commercialisation of the sequence. Left unaddressed these aspects will prevent good products from ever reaching the market. A reality that we continue to ignore in South Africa is that academics generally invent and entrepreneurs innovate. At the minimum, both of these sectors are required to bring about the transformation of sequence to product. Healthy and sustainable partnerships that are fostered between the academic, private and public sectors can be a key enabler in order to allow patients to benefit from research.

---

## FUTURE VIEW

*Keynote Presentation:*

**Genetic testing services in emerging economies: the GenTEE (Genetic Testing in Emerging Economies) project**

**I Nippert** (Women's Health Research, Muenster Medical School, Westfaelische Wilhelms-Universitaet, Muenster, Germany), A Christianson (Division of Human Genetics, National Health Laboratory Service & University of the Witwatersrand, South Africa), DDG Horovitz (Centro de Genética Médica - Instituto Fernandes Figueira/Fundação Oswaldo Cruz, Rio de Janeiro, Brazil), R. Kamal Raouf (IPGCS/ Ain-Shams University, Cairo, Egypt), C. Padilla (Department of Pediatrics, College of Medicine and Philippine General Hospital; Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila, Philippines), V. Penchaszadeh (Centre of Genetics and Public Health. Department of Health Sciences, Universidad Nacional de La Matanza, Buenos Aires, Argentina), A. Rajab

(Genetic Unit, Directorate General of Health Affairs, Ministry of Health, Muscat, Sultanate of Oman), I. C. Verma (Centre of Medical Genetics, Sir Ganga Ram Hospital, Rajender Nagar, New Delhi, India), N. Zhong (Peking University Center of Medical Genetics, Beijing, People's Republic of China), L. Gribaldo (Institute for Health and Consumer Protection, European Commission Joint Research Centre, Ispra, Italy), U. Kristoffersson (Department of Clinical Genetics, University Hospital Lund, Lund, Sweden), J. Schmidtke (Institute of Human Genetics, Hannover Medical School, Hannover, Germany)

Background: Due to the epidemiological transition in the emerging economies of China, East Asia, India, Latin America, the Middle East and South Africa, these countries are facing (i) an increasing proportion of morbidity and mortality due to congenital and genetic conditions, (ii) a rising need for genetic services to improve patient outcomes and overall population health.

Objectives: (i) to document and compare current practices and the state of genetic service provision in Argentina, Brazil, China, Egypt, India, Oman, Philippines and South Africa, (ii) to identify current knowledge gaps and unmet service needs, (iii) to inform policy decisions for the challenges of delivering equitable high quality genetic services and to promote international collaboration for capacity building.

Methods: A standardized survey that is the first of its kind worldwide that allows comparison of services internationally across a number of key dimensions by using a core set of indicators, selected by the GenTEE consortium for their relevance and comparability. The survey maps the current state of genetic services and identifies current drivers, barriers and opportunities for genetic services development.

Results: Although, GenTEE countries have put resources into genetic/genomic research during the last decade and some countries have developed cutting-edge research capacity, significant gaps exist in the translation of such research into routine public health services. There is no equitable access to genetic services in all countries due to financial barriers (underfunded fragmented public services, out-of-pocket expenses tend to be the norm for genetic testing services), geographical barriers (concentration of services in main cities) and skill gaps, resulting in inequitable services or delayed access. The development of services in the private sector is mostly opportunistic and technology and market driven.

Conclusion: International collaborative networks can facilitate capacity building and help to strengthen the provision of quality genetic/genomic services.

---

**OP 33**

**Planning for Health in the Post-Genomic Era in Africa**

**R Ramesar** (University of Cape Town)

Several projects in the South African context, concerned with human genetics, have been shepherded from basic research to translation, and been of utility in the clinical environment. Examples of these include a project on colorectal cancers in the Western and Northern Cape Provinces, a national Retinal Degenerative Diseases programme, Neurodegenerative Disorders projects, amongst others.

An unprecedented effort is currently being made through the Human Hereditary and Health: Africa (or H3A) programme in order to encourage networks of genomics research on the continent of Africa, covering both infectious and non-communicable diseases. This very welcome 'intervention' by the National Institutes of Health (USA) and the Wellcome Trust (UK) is dedicated to systematically develop research capacity on the continent, while addressing the genuine issue of expanding the applicability of genomics to diseases of importance in different parts of Africa.

This presentation will review projects that have shown utility and sustainability through their translation in our setting in Cape Town, and highlight the limitations of even successfully translated research. Our experience is that there are a number of limitations in translating our research, despite its obvious health benefits in terms of decreasing morbidity and mortality (i.e. emerging from our colorectal cancer research) The role of trans-disciplinarity being nurtured as part of the larger 'genomic' enterprise on the continent, as a means of seeing the full value chain of research towards translation will be highlighted. This would usually involve plotting all stakeholders and ensuring their participation from the earliest design processes in research.

---

**OP 34**

**Raising public awareness of genetics: responsibilities and resources**

**V Corfield** (Stellenbosch University)

The responsibility of scientists to translate genetic research findings and their implications to a wider public audience was emphasised more than two decades ago with the Human Genome Project's ELSI, an initiative to promote discussion of ethical, legal and societal issues. In May 2013, the European Society of Human Genetics issued a press statement concerning coping with the application of advances in genetic sequencing analysis that included the statement "Only with the benefit of a general increase in genetic literacy can society become properly involved in the debate over who has the right to know what and in which circumstances". National and international research agencies require their awardees to include a "public outreach" component. Translating genetics to the South African public and to clinical genetics patients and their families poses particular challenges, given multicultural, diverse language and disparate educational backgrounds.

Numerous effective, internet-accessible, low-cost resources exist to help clinicians and scientists translate genetics "sci-speak" to "street-speak" to a range of audiences.

The author will review some of the available resources and discuss her experiences in their use in engaging the general public of all ages, in rural and urban settings across South Africa, and in Namibia and Bahrain, as well as lay-interest groups (albinism and monogenic cardiac arrhythmias). Formal and informal evaluations have been applied to ensure their relevance and acceptance to target audiences.

Raising awareness of genetics among a wider audience using varied resources will inform the public debate on the ethics of the application of new-age technologies.

---