National Centre for **Medical Genetics**
Ionad Náisiúnta **Gineolaíocht Leighis**

National Centre for Medical Genetics Annual Report 2012

National Centre for Medical Genetics
Our Lady's Children's Hospital
Crumlin
Dublin 12

www.genetics.ie

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1 Foreword by Professor Andrew Green

I am delighted to introduce the 2012 report of the activities of the National Centre for Medical Genetics. This report gives a description of the clinical and laboratory work of the centre, as well as the active research and teaching programmes in the Centre. It reflects the challenging and difficult economic circumstances for those whose role it is to provide care for families affected by genetic conditions.

Despite the reduction in staff of the NCMG, as a result of the financial situation nationally, the NCMG has increased the number of patients seen in its clinics since 2011, and has an exceptionally high attendance rate for its clinics, with only 7.7% of appointments not attended. Nonetheless, as result of an increasing number of referrals to our clinics, and the resultant excessively long waiting times, we have regrettably had to introduce restrictions on some of the types of conditions that we can see in clinic.

Both cytogenetic and molecular genetic laboratories can be justifiably proud in maintaining accreditation from CPA (UK) in 2012. Both laboratories were highly commended for their work, and I congratulate all the laboratory staff, especially the quality managers Adam Dunlop and Christine Brady for their hard work in achieving and maintaining standards.

Nonetheless, there is much more that could be done. The clinical service of the NCMG is deeply under-resourced, with only 15-20% of the staffing levels of other European genetic centers serving a similar population size. Waiting times for families to be seen in the genetics clinic are unacceptably far too long. There are many samples being sent abroad for genetic testing from Irish patients costing well over 1 million euro, when those samples could be tested in the NCMG at a lower cost, if the NCMG had adequate staff and equipment resources to carry out those tests. The HSE has identified the issue of genetic tests being directly sent out abroad without oversight as a significant risk, which was placed on the HSE risk register in 2012. Repatriation of those tests would be of benefit both to the exchequer and to Irish patients with genetic diseases, as their clinical geneticists are dealing directly with the laboratories carrying out the tests.

The NCMG has close links with the many support groups for families with genetic disorders, and in particular with GRDO, the Irish Genetic and Rare Disease Organisation. We are grateful for their support, and look forward to continued close relationships with these groups, particularly leading into 2013, when the EU directive on Rare Diseases must be implemented.

I would like to thank in particular all the staff of the NCMG who have helped put together this report, in particular Dr Sally Ann Lynch, and Christine Brady. I would also personally like to thank all the administrative, laboratory and clinical staff of the NCMG for all their unstinting hard work over the last year for patients and families affected by genetic disorders.

Andrew Green
Director, National Centre for Medical Genetics, November 2012.

2 Introduction

This comprehensive report provides an insight into the specialist work carried out in the National Centre for Medical Genetics (NCMG) in 2012. The data was compiled by nominated staff members from each division who felt it important to highlight our work & achievements and make it available to our users. It shows the changes in demand and highlights the challenges that our national service has had and continues to face. It has now been endorsed and supported by the Director and the laboratory heads of NCMG

The NCMG has been based in Our Lady's Children Hospital in Crumlin (OLCHC) since its inception in 1994. Since this time, the NCMG has obtained its funding directly from OLCHC and its staff form part of the overall staff numbers of the Hospital. Therefore, despite having the responsibilities of a National service, our funding has not been ring-fenced. Overall funding for the NCMG has not been related to the year on year increases in clinical or laboratory activity. Recruitment and retention of NCMG staff numbers is outside the control of the Centre. This has had a significant impact on the services offered by the NCMG, both in the past and especially in recent years due to the economic climate and employment moratorium. These factors have resulted in the cessation and/or reduction of specific services. In response, there has been ongoing discussion by the NCMG with OLCHC, the Health Service Executive (HSE) and especially with the National Hospital's Office (NHO) (which was disbanded in 2009) at the HSE to highlight and address these service difficulties. This has resulted in engagement with the NHO/HSE for a 'Needs Assessment' for Medical Genetics services in Ireland and an assessment of the resources required for the proper provision and organisation of a national medical genetics service.

2012 has been challenging for any service trying to provide health care within the Republic of Ireland. NCMG is no exception particularly as we are the only centre providing Clinical Genetics services in the Republic of Ireland. NCMG strives to follow best practice as outlined by the Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG). However, we have experienced staff cutbacks of between 15-25% throughout these years and have had to curtail some services as a result.

Safe practice is of utmost importance. NCMG has had to limit what it can offer in terms of genetic testing whilst our resources have been cut. Whilst reducing what we can offer in terms of service and testing has been a difficult decision to make, it has only been undertaken when the volume of requests became so overwhelming that patient safety was being compromised.

At the end of 2012 there were 65 employees (59.08 WTE) working in NCMG. This includes 9 administrative staff members who provide essential support to our team. In addition, there were 4 Genetic Counsellors with honorary contracts / charitably funded posts, 3 research posts based in NCMG, and 3 volunteers/students on work placement. There are three divisions in the NCMG (http://www.genetics.ie); each is individually distinct and unique. These are:

- Clinical Genetics (http://www.genetics.ie/clinical/)
- Cytogenetics (http://www.genetics.ie/cytogenetics/)
- Molecular Genetics (http://www.genetics.ie/molecular/)

3 Division of Clinical Genetics

The Clinical Genetics team consists of Consultants in Clinical Genetics and Genetic Counsellors who are experienced practitioners with a scientific or nursing background and a Professional qualification in Genetic Counselling. Consultants see all cases where a diagnosis is still being sought and complex cases. Genetic counsellors see families where the diagnosis is already established to discuss recurrence risks, possible preventative or reproductive options and any implications for more extended family members. A significant proportion of the Genetic Counsellor case-load involves predictive testing for certain later-onset conditions. In addition, Genetic counsellors coordinate specific pre-natal tests in families known to our service. As a national service, the clinic appointments and any genetic testing arising is free. The NCMG holds clinics in two major paediatric hospitals in Dublin – Our Lady's Children's Hospital Crumlin, where the centre is based, and The Children's University Hospital, Temple Street. Peripheral clinics in Cork, Galway, and Limerick are held regularly throughout the year. Cardiac genetic clinics are held at Heart House (Mater campus) and Tallaght Hospital, as well as in the NCMG.

The Clinical Genetics Committee of the Royal College of Physicians in London defined three objectives of a clinical genetic service: (1) for persons who are affected or who are referred because of a genetic risk - to make the genetic diagnoses, provide pedigree analyses and assess the transmission risk. These are necessary for genetic counselling and to guide preventive and therapeutic actions; (2) to support the identification and surveillance of relatives who are at risk for serious genetic disorders, but who may not have been directly referred, so that they may receive well informed genetic counselling and guidance on preventive and therapeutic actions if required; and (3) to provide support to family members, both to those affected and unaffected.

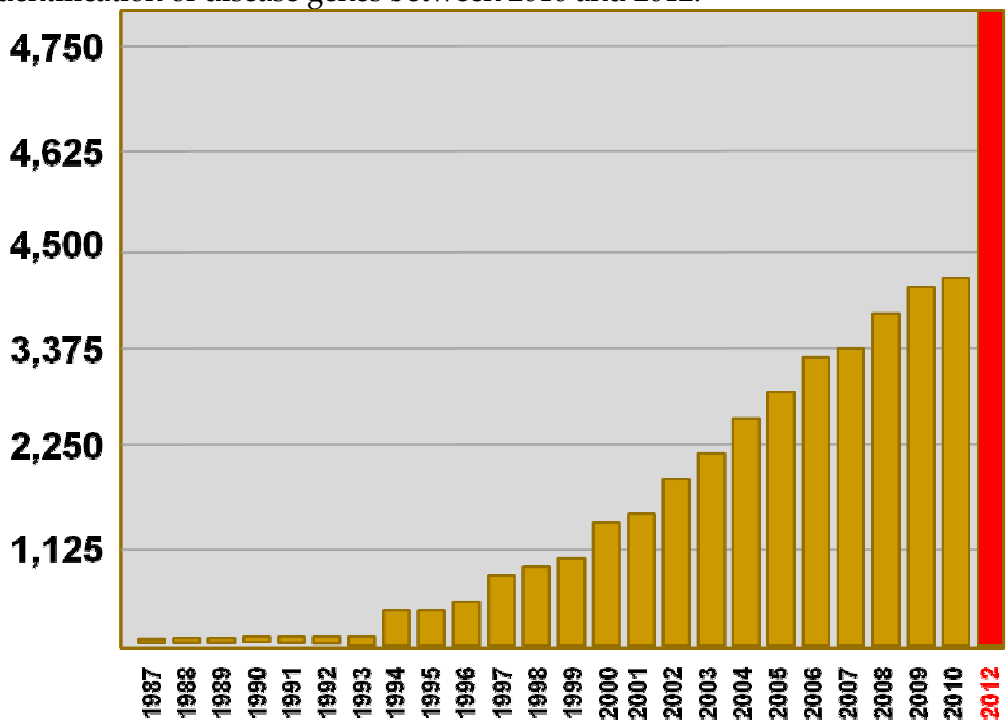
The British Clinical Genetics Society (2000) outlined in detail the responsibilities of a clinical geneticist. Particular emphasis was placed on follow-up, support, coordination of health surveillance, and services to extended families. Unfortunately, with staffing levels at 80-90% below other centres in Europe NCMG has had to focus on our core role, that of diagnosis, pedigree analyses and estimate of transmission risk. Most UK units have disease specific registries to help coordinate the care of patients with rare diseases but a database manager is a requirement and NCMG, with limited administrative support, cannot provide this.

3.1 Referrals

Clinical Genetics (http://www.genetics.ie/clinical/) as a speciality, involves the care of both children and adults with over 40% of our referrals being for adults. The NCMG has a broad referral base with referrals from a wide range of specialties including obstetricians; surgical specialities such as orthopaedics, plastic surgery, general surgery, ophthalmology, ENT; paediatric specialities such as metabolic medicine, neonatology, neurology, endocrinology,

cardiology, immunology, dermatology and gastroenterology; the adult equivalents of each of these specialities; GPs and allied health professionals. Around 70-80% of rare diseases are genetic and we are cognisant of the EU recommendation on the treatment of patients with rare disease which Ms Mary Harney signed in 2009 and which comes into place in October 2013.

The use of genetic techniques and approaches is increasing in all clinical specialties, but the recent report prepared by the Royal College of Physicians of London indicated that many primary care physicians and specialists in other fields do not feel confident to handle genetic issues and greatly value the support of clinical geneticists. The number of genes available to test has risen exponentially over the last ten years. As the technology increases in sensitivity so more genetic variants are being identified including those of uncertain clinical significance requiring specialist knowledge. This has been reflected in the nature of our referrals and we have noted a concurrent increase in the number of referrals generated by clinicians (paediatricians, cardiologists & obstetricians) asking us to help with interpretation of laboratory results. This has been noted by Genetics centres throughout Europe. The graph below details the massive increase in the identification of disease genes between 2010 and 2012.



3.2 Restrictions on Clinical service

Regrettably, in February 2012, the clinical team at NCMG had to introduce introduce restrictions to its service as one of the consultants was going on maternity leave for 12 months and we were only awarded a locum of 0.4 whole-time equivalent which provided cover for the cancer aspect of the job only. The clinical team weighed up the various options in trying

to manage an increasing waiting list (already at >12months and likely to rise significantly). We were alert to the EU recommendation on Rare Diseases, due to come into action in October 2013. We were also alert to our referrers who had referred patients at high risk of recurrence not being able to understand why it would take us ~18 months to get to see these high risk families. We had an onus to prioritise families that had greater need to be seen than others despite how uncomfortable this was to consider.

With this in mind, we decided the safest option was to put restrictions on certain genetic disorders that were not rare. We therefore are currently no longer accepting referrals for the following disorders:

- Trisomy 21 non-disjunction type. We still see families with translocation trisomy 21
- Isolated Neural Tube Defects
- Non-syndromic cleft lip/palate
- Non familial sensori-neural deafness

Some of these conditions have well established patient support groups plus the local paediatric and nursing teams have a huge experience in dealing with these conditions e.g. Trisomy 21 & NTDs. We felt that these teams could pick up part of what we offer and we have helped in this regard by producing a letter detailing recurrence risks for Trisomy 21 families in place of an appointment. All cases of Spina bifida are seen in Temple Street and we have produced a leaflet in conjunction with the local team in Temple Street that can be given to families which details their recurrence risk and provides information about folic acid.

The Dublin Cleft Centre which encompasses Cleft teams from Temple Street & OLHC also has a strong multidisciplinary group in place. Their goal is to provide a service that matches the recommendations of the Clinical Standards Advisory Group (CSAG 1998). The British clefting units all received funding specifically earmarked to provide genetic services for cleft families from the NHS. NCMG did not and had taken on the work with no extra staff. The removal of our service means the Dublin cleft teams no longer meet CSAG standards and this is a regret for us. We understand our colleagues concerns that our restrictions have directly impacted on their aim to reach best practice guidelines & international standards but with staff levels that are the poorest in Europe we cannot provide a similar service to the UK, see figure 1-3. We plan to develop a new Cleft Lip and Palate genetics leaflet for the Cleft teams which can be provided to parents by clinicians in the near future.

Non familial sensori-neural deafness

Traditionally NCMG accepted many referrals for deafness for baseline investigations. In other countries, these investigations are normally done by the local paediatricians or clinical

audiologist. Clinical audiology as a speciality is not developed in the Rep of Ireland and hence these referrals came our way. There is a huge amount of work involved in the baseline investigation of these children & adults and we were unable to perform many of the investigations as we do not have the capacity or the correct environment to offer these (e.g. audiograms, ECGs etc). Also, some cases of hearing loss are due to non-genetic causes and we felt we were under investigating these families as some of the non-genetic investigations were not included.

Before introducing restrictions we met with consultant paedatiricains and ENT surgeons and developed simple workable protocols on the investigation of deafness which could be used by paediatricians all around Ireland. These are based on the American and British protocols. We have been sending back all deaf referrals to the referrer with a copy of this protocol and a recommendation to refer to their local paediatrician. In the case of a deaf adult it is the local referrer's responsibility to organise the investigations. Whilst the current system is not satisfactory, we do think it has highlighted a need for a dedicated paediatrician/clinician with an interest in deafness to lead on this. Ultimately, we do feel that the current system is an improvement on what was before although there is a huge deficit in the management & investigation of deafness in comparison to other European countries.

3.3 Triage of referrals

We introduced triage of clinical referrals to NCMG at the same time as the restrictions to service were introduced. The aim was to standardise the referral process, to bring equity to referrals, to improve the quality of referrals and to ensure that wherever possible, genetic tests that could be carried out prior to clinic were done so that patients could be dealt with at one visit wherever possible. Triage is also recommended by the Special Delivery Unit in the HSE and all HSE clinical teams are meant to engage in this process by 2013.

Triage is carried out jointly by one consultant and a genetic counsellor. An audit of this process was carried out late on in 2012 which revealed that 30% of referrals are put "on hold" with requests to the referrer for either more information or for initial blood genetic test to be done prior to the appointment. Many of these had genetic testing done but the report was not included with the referral and NCMG cannot see families without a copy of the genetic test report.

A small percentage of referrals (6%) were rejected, most because they had one of the 4 disorders listed in the list of conditions in 3.2. above We have noticed that as referrers have become aware of our restrictions their referral numbers have dropped.

What happens to the referrals kept on hold?

A Genetic counsellor is assigned on a monthly basis to managing the follow up of all triage cases that have been put on hold. They link reports with referral letters and allow these to be

removed off the hold list onto the waiting list once all the documentation that was required had been received.
Where our request for further information of bloods has not been undertaken we write a letter 6 months after the request informing the referrer that as we have not received the necessary information the referral is now being rejected.

Priority cases
We have identified certain cases where we give priority to couples:
Couples at 1 in 4 (or higher) risk of recurrence of a child with a genetic condition. These patients swill be offered an appointment sooner than the routine 12 month waiting time.

A number of changes to our practice ensued, for some conditions testing is carried out by GPs or referrers. These conditions are strictly those where the test result, if positive has no health implications for the patient themselves. Those patients who test positive are offered an appointment, those that test negative are sent a letter. We requested blood tests prior to clinic in approximately 16% of referrals. We arrange blood tests done on at risk relatives for certain conditions: e.g. chromosomal translocations & carrier testing for autosomal recessive disorders (e.g. cystic fibrosis). Whilst, this saves appointments it is not considered best practice by other European countries so we have reservations and are keeping this under review. On balance, we felt that relatives of our families who faced a high risk of having a child with a serious medical condition would prefer to have a blood test up front and be seen if the test was positive (turn around time ~4/5 months rather than wait >12 months to be seen before any blood was taken and then have to wait a further 3 or 4 months for a result (total 16-22 months). Please note, we do not offer this to any patients where the family disorder would require predictive genetic testing (e.g. the test result has direct health implications for the patient). These families require an appointment prior to testing.

Administration following referral
Whilst triage is an important step for NCMG to have made, it is proving to be very time consuming. Most of the administration has had to be done by the clinical team as our administrative staff are over-stretched. It has also been difficult to document the amount of time and effort spent throughout this process. In particular, whilst a lot of work is done arranging for blood samples to be taken by GPs or phlebotomy clinics in outside hospitals, if the patient tests negative and receives a letter, the work that we put into this is not recorded as clinical activity by health authorities although it is hugely beneficial not only to that patient but also all others on the waiting list.

3.4 Clinical Activity

Between 2006 and 2010 the number of referrals for the NCMG Clinical service has increased by 27%. This represents an average yearly increase in referrals of 6.75% per year between 2006 and 2010. We have seen a drop in 2011 and again in 2012 which may reflect the introduction of our triage system in this period. These figures are outlined in Table 1

Table 1

Table 1	2008	2009	2010	2011	2012
NCMG referrals	4,433	4,919	4,862	4,580	3,157

Table 2

Table 2	2010	2011	2012
Total appointments	2,628	2,765	3,004
OLCHC OPD	1,278	1,438	1,509
Temple St OPD	408	308	424
Cork	302	251	330
Limerick	170	211	208
Galway	129	122	136
Other		153	180
Did not attend	267	243	252
Did not attend rate	9.2%	8.9%	7.7%
In-patient consultations			
OLCHC	237	179	137
Temple St	75	61	48
Maternity Hospitals	29	42	32
Total patients seen	5,648	5,937	5,815

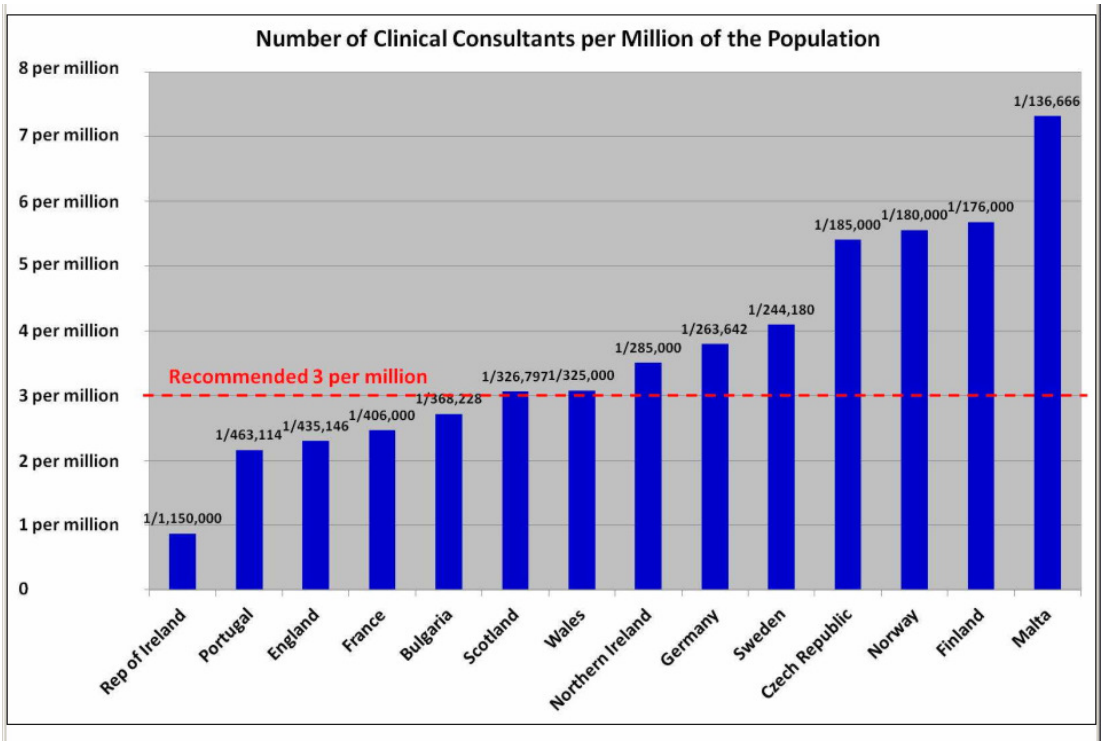
The clinical activity is outlined in Table 2 for the years 2010 to 2012. The numbers of attended appointments has increased, and the numbers of patients attending has remained stable. The

outreach clinics in Cork, Limerick and Galway continue unchanged. The percentage of patients not attending has decreased to below 8%, which is well below the national average of 15%. This low DNA rate is a tribute to the administrative staff of the centre, who proactively contacts families to ensure patient attendance.
Genetics clinics are unique as we deal not only with the individual patient referred but with the family unit and our clinics include family appointments. Therefore OPD clinic numbers refer to the numbers of appointments attended, and not the number of patients seen. On average, 2.5 family members are seen at each clinic appointment. Each clinic appointment in the NCMG generally takes between 45-60 minutes of patient contact. Approximately 75% of these contacts are new referrals which are in contrast to many other outpatient clinical services where a significant proportion are follow up appointments. The number of patients seen annually is shown on the final row of figures for each year.

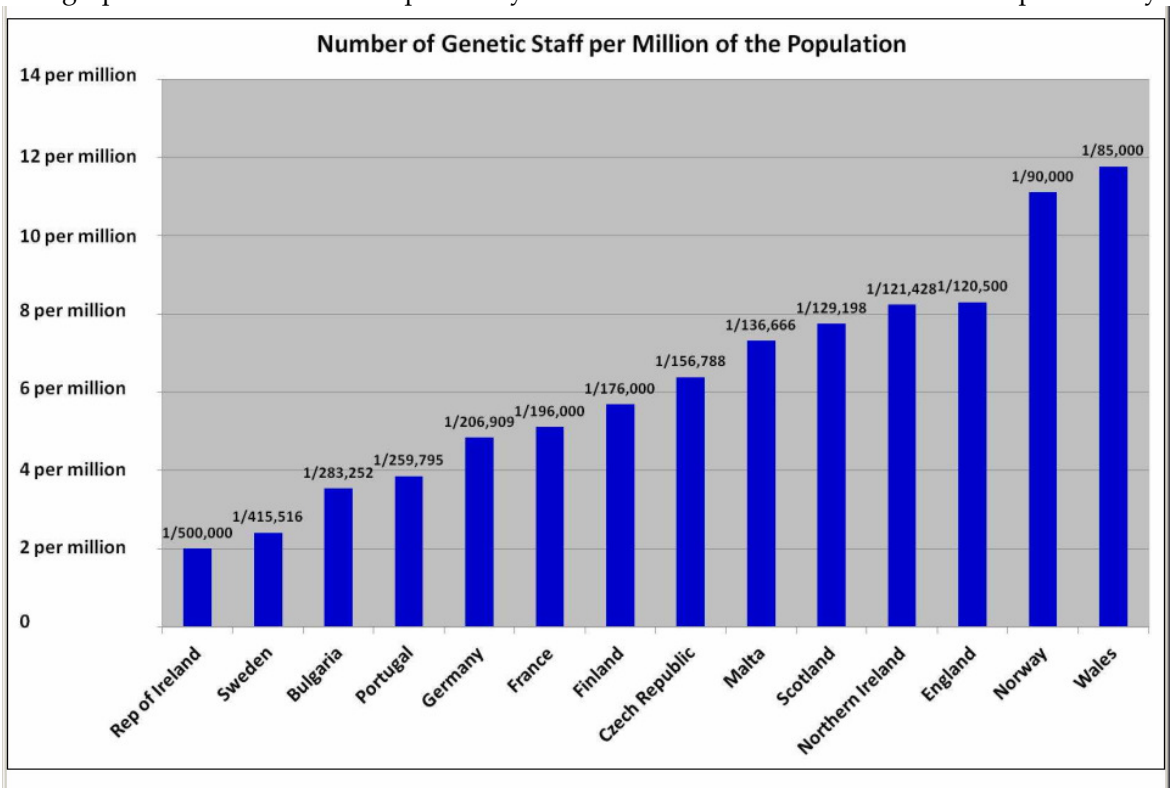
The 151 appointments in 2011, and the 180 appointments in 2012 in a venue marked "other", reflect the work done by Nicola Harper, who is a charitably funded genetic counsellor appointed in 2011, who sees patients not only in the NCMG, but also in Heart House attached to the Mater Misericordiae University Hospital, Eccles St, and the Cardiac Risk in the Young (CRY) unit, in Tallaght University Hospital.

3.5 Staffing levels

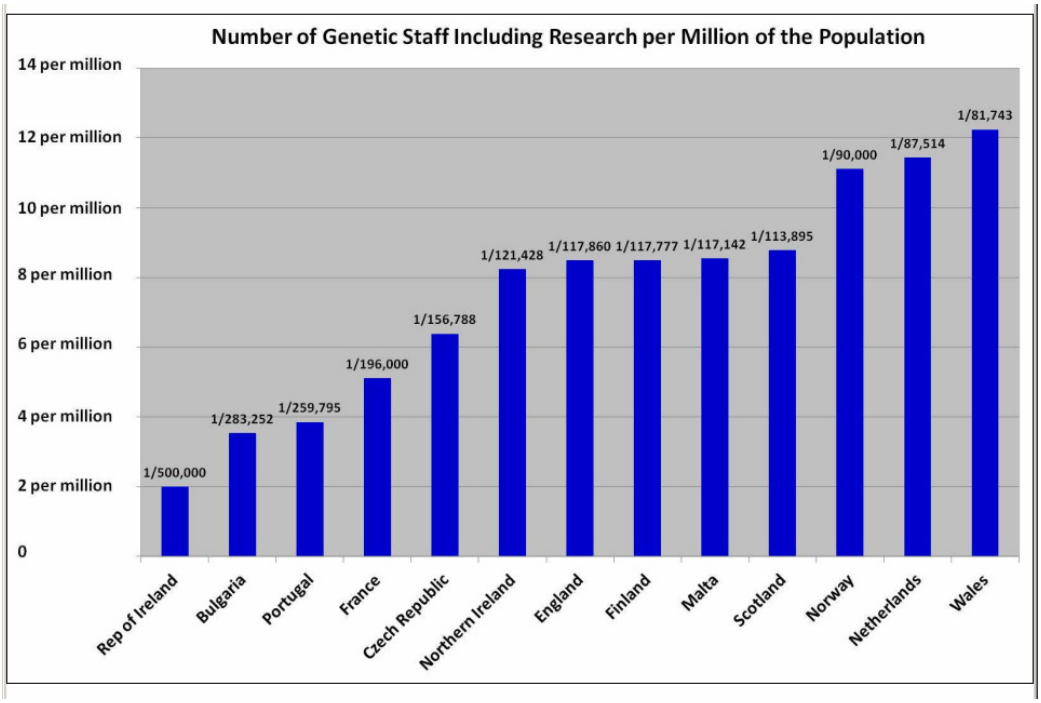
The European Society of Human Genetics (ESHG) highlighted poor clinical genetic staffing levels in the Republic of Ireland at the opening plenary session of their annual meeting in Nurnberg June 2012. The Royal College of Physicians UK recommend a minimum of 3 Consultant Geneticists per million and the Association of Genetic Nurse and Counsellors UK (AGNC) recommend 6 fulltime Genetic Counsellor per million population. Based on these recommendations, a population of 4.6 million the Republic of Ireland should have 14 Consultant Geneticists and 28 Genetic Counsellors. In fact there are 4 full time consultant geneticists and 5 whole time equivalent genetic counsellors funded for the country, which means that Ireland has the worst staffing ratios for genetic specialists in Europe https://www.eshg.org/111.0.html. We also have 1.5 WTE charitably funded genetic counsellors, one full time for cardiac genetics (funded by CRY, Heart House and CMRF), and one part time for neurofibromatosis (funded by the Neurofibromatosis association). NCIMD employ a part-time genetic counsellor to help with the metabolic case load who has an honorary contract with NCMG, this post is funded by pharma (Shire pharmaceuticals).
Dr Lynch spoke at the ESHG council meeting and the council agreed to host a workshop on inequality in genetic health at the 2013 ESHG meeting in Paris. Dr Lynch agreed to collect European staffing data as a comparison to highlight our problems. The graphs below have been created as a result.



This graph details the number of publically funded Consultants in Clinical Genetics per country



This graph details the number of clinical genetic staff (including consultants, medical Doctors in training (Specialist registrars) and genetic counsellors)



Training in Clinical Genetics

On 30th August 2012, the HSE formally sanctioned a training post in Clinical Genetics. This training post had taken several years to come to fruition. As we have close links with the National Centre for Inherited Metabolic Disorders (NCIMD), we proposed to offer a dual training programme in both Clinical Genetics and Biochemical Genetics. The post will be over four years. If the trainee wishes to sub-specialise in Biochemical genetics they will need to spend more time in this field. The fist trainee is due to start in July 2013 commencing in Biochemical Genetics and then transferring to NCMG in January 2014. Dr Sally Ann Lynch will act as the National Speciality Director. Prof Green & Dr Gill are nominated trainers and Prof Eileen Treacy is also a nominated trainer and will be responsible for the biochemical training.

3.6 New Staff posts

There were no additional clinical staff posts for the NCMG in 2012.

We welcomed Dr David Gallagher, consultant in cancer genetics, as a 40% maternity leave locum for Dr Gill in 2012. Dr Gallagher brought expertise from Sloan Kettering Memorial Centre in New York, where he trained, and carried out cancer genetics clinics in the NCMG.

Ms Claire Kirk was appointed in 2012 as a charitably funded part time genetic counsellor dealing with families with neurofibromatosis. Ms. Rosie O'Shea started as a part-time genetic counsellor funded by SHIRE Pharmaceuticals to set up a genetic counselling service in NCIMD.

3.7 Prenatal testing

Prenatal testing is available in 6 fetal medicine units in the Republic of Ireland (the 3 Dublin maternity hospitals, Cork, Limerick & Galway). NCMG are closely involved in those families at increased risk of a specific genetic condition. We co-ordinate approximately 100 tests per annum in conjunction with the 3 Dublin maternity hospitals and we expect this to rise significantly as the availability of testing increases. It is not feasible to arrange prenatal tests for rare disorders outside of Dublin as co-ordination of sample collection and timely transport (sometimes through customs) for subsequent analysis by NCMG or laboratories abroad precludes this. The work-load involved in these cases is significant requiring close and sensitive liaison between the Genetic Counsellor, the family, the obstetric team, the NCMG laboratory and the testing laboratory (if the samples are being sent abroad). Many of these cases are co-ordinated by phone and letter and therefore this clinical activity remains largely uncaptured.
Ms Rosie O'Shea, Genetic Cousellor carried out a three year review of pre-natal cases from 2010 through to mid 2012.This showed a yearly rise in prenatal requests from 68 in 2010 to 80 in 2011 and 68 until mid 2012 and increasing. For 2011,101 consecutive requests for pre-natal testing over the last 12 months. The commonest reasons were for Cystic Fibrosis, Sickle Cell Anaemia and Duchenne Muscular Dystrophy (combined 30/101 [30%]), all serious disorders with a high (1 in 4) recurrence risk. In total, 54/101 (53%) had a 1 in 4 recurrence risk, 2 had a 1 in 2 risk of recurrence and 18 were requests for chromosomal translocations-with varying recurrence risks. 26/101 (26%) had low recurrence risk (1% or less).

3.8 Genetic Counsellors

The following genetic counsellor successfully completed registration with the Genetic Counsellors Registration Board (GCRB) in the UK. Rosie O'Shea (2012); Rosemarie Kelly re-registered in 2012.
Genetic Counselling registration is important to maintain continuous professional development with GCRB renewal required every 5 years. The GCRB have recommended that the registration number is on clinical correspondence.

Genetic counselling students attending NCMG for 2012 were Eoin Hanney (Cardiff), and Claire Shea-Stokes (Manchester).

Nicola Harper presented at the AGNC 2012 on "The complexity of counselling for double or compound heterozygosity in inherited cardiac conditions". She also took part in a National Cardiac Audit of the UK and Irish services, with Ireland having one of the highest response rates. Nicola's post is charity funded by National Children's Research Centre, The Mater Foundation and CRY Ireland.

Genetic Counsellors continue to maintain close links with parent support groups. Rosemarie Kelly presented to the Turner Syndrome group in Ireland (TCGI) (April 2012). Jacqueline Turner continued her involvement with Muscular Dystrophy Ireland by presenting a lecture to the Limb Girdle Muscular Dystrophy support group on 29th of September.

Jacqueline Turner attended the first conference held by the Irish Angelman syndrome Support group in Croke Park on Sunday the 13th of May. Jacqueline Turner also attended the conference for Metabolic Bone Disease in Children on June 22nd, which focused on children with Osteogenesis Imperfecta.

Claire Kirk, NF Genetic Counsellor, presented an NF Clinic update at the Neurofibromatosis Association Ireland (NFAI) AGM in April 2012. She was involved in the development of a range of NF information leaflets in liaison with the NFAI.

Alana Ward, Genetic Counsellor with a specialist interest in Cystic Fibrosis (CF) gave a seminar at the CF Association Ireland (CFAI) annual conference in April, 2012 in Wexford.

An article entitled 'Genetic Counselling and CF newborn screening' appeared in the April/May edition of the CFAI Spectrum magazine. An information sheet about Genetic carrier testing for CF was developed in conjunction with the CFAI to help disseminate information and advice to members and their families. Two presentations were given to update Paediatricians on the first anniversary of the CF newborn screening program at Grand Rounds in the Children's University Hospital, Temple Street (August, 2012) and Grand Rounds in Our Lady's Children's Hospital Crumlin (November, 2012).

Alana Ward and Jacqueline Turner continued to have a biannual commitment to tutorials to Medical students attending UCD.

Jacqueline Turner also lectures twice yearly to Nurses taking part in the Level B programme 'Caring for a child with a life limiting condition' in Our lady's Children Hospital.

Cancer Genetic Counsellors gave a number of presentations to Oncology Nurse Students. Nuala Cody presented to the Mater Oncology Nurses studying for their Masters program in Oncology nursing. Marie Meany presented in UCD to the Oncology Nurses studying their general nursing degree program. Nuala Cody attended a multidisciplinary meeting in the National Cancer Control Program in May 2012 to discuss the future for Cancer Genetics in Ireland. Marie Meany volunteered to become part of that working group in helping to implement Family Risk Assessment clinics in eight Oncology Centres of Excellence in Ireland. Nuala Cody attended a study day organised by Nowgen Centre in Manchester on Familial bowel cancer study day in October 2012.

3.9 Clinical links with other genetic & other specialist departments

The clinical team at NCMG have two joint meetings annually with the Clinical Genetics department in Belfast. Presentations are made by staff from both genetic teams. Initially these meetings alternated between both centres but since 2010 the meetings have been held at the paediatric department at Daisy Hill Hospital Newry with the kind assistance of Dr James Hughes. All meetings receive Continuing Medical Education (CME) approval.
Additionally from 2008 to the present day, both Professor Andrew Green and Dr Sally Ann Lynch attended the multidisciplinary paediatric endocrine meetings held three times a year and hosted by the paediatric endocrinology teams at OLCHC and Temple Street Children's Hospital. Bi-annual joint meetings are also held with the Paediatric Dermatologists. In addition, Dr Lynch attends the cross city paediatric neurology meetings held quarterly. Prof Green or Dr Gill attend the tumour board meetings at OLCHC.

3.10 Clinical Risk from poor quality Genetic testing

Dr SA Lynch together with Ms Anne Marie Keirnan submitted a full NCMG risk assessment document on poor quality genetic testing to the HSE in May 2010. The methodology applied to the risk assessment process was based on the principles of the Health Service Executive Risk Assessment Tool and Guidance (2009), OLCHC risk management documents and the National Patient Safety Agency. This document outlined issues to do

1. Quality of reports from some international centres not meeting international standards

2. Unnecessary splitting of family samples for testing in multiple laboratories

3. Failure by clearing house laboratory to triage samples

4. NCMG have limited working knowledge of the foreign laboratories used by clearing house laboratories to complete testing and generate the reports used in NCMG to provide genetic advice

5. Referrals to international laboratories made by non-geneticist clinicians, that may require consent under Irish law, which won't be apparent to the testing laboratory nor the non-Genetic clinicians.

The HSE contacted OLCHC and ultimately NCMG in June 2012 regarding whether this issue had been resolved. Clearly, we had stated that all measures we could put in place to control any clinical risk had already been dealt with and highlighted in the 2010 report but as NCMG had no jurisdiction over what clinicians in the rest of the Republic of Ireland order in terms of genetic testing this issue still remained. We highlighted to the HSE once again that this was a problem that only they could control and re-submitted a "Template for Escalation of Risks to next level Governance structure" form in July 2012. In December 2012, the HSE acknowledged the NCMG risk assessment reports findings and put this issue on the Dublin mid-Leinster "at risk" register. We await any action by the HSE to address our concerns. A copy of the NCMG risk assessment report is available by request through the www.genetics.ie contact form. Please address the query to Dr SA Lynch.

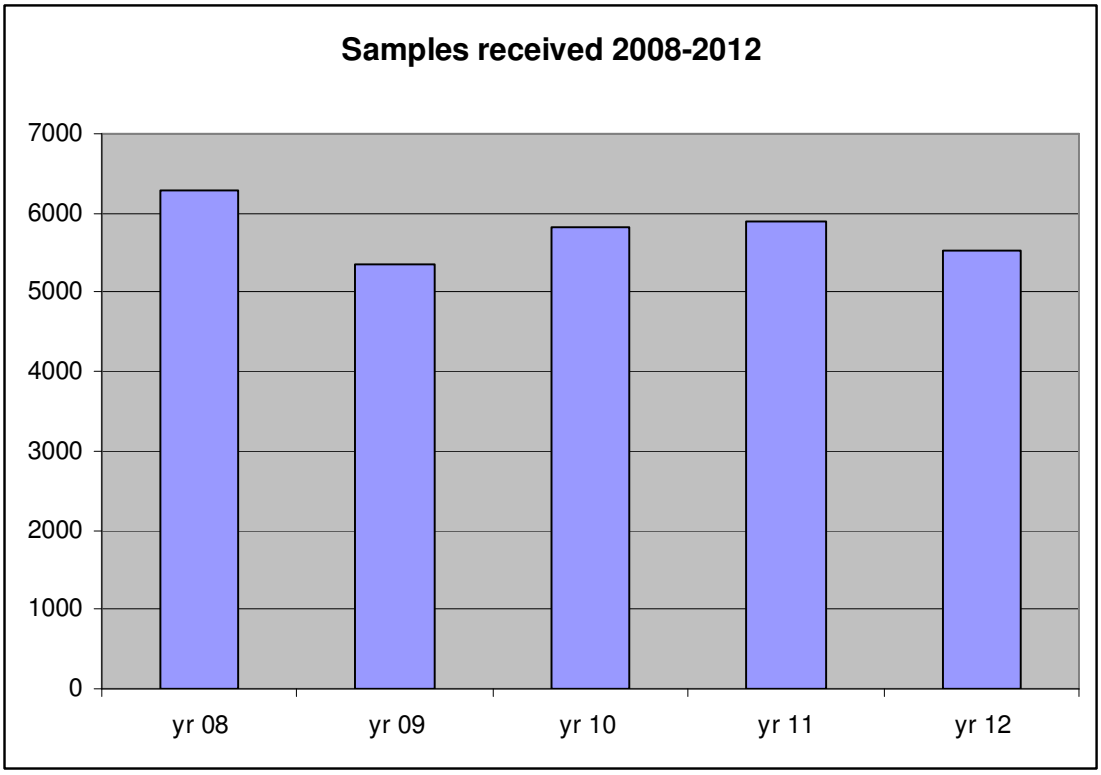
4 Division of Cytogenetics

The Division of Cytogenetics continues to strive to provide the fullest diagnosis service possible within the constraints of available finance and staffing. To achieve this there remains the unfortunate scenario that sample numbers need to be controlled to ensure timely reporting of results and avoiding increasing backlogs. A review of 2012 shows, in retrospect, that ultimately it represented a holding year in the Division of Cytogenetics with preparations made for changes in 2013. At the start of 2012 it was anticipated that an in house microarray service would have been introduced during the middle of 2012, however, unforeseen events resulted in a delay in this introduction. These events will be discussed in more detail in the relevant section below. Otherwise, the Division had no major changes planned and 2012 focus of only maintaining existing services to the same or improved quality level and address finances with the view to cost savings in addition to those already achieved in 2011.

4.1 Sample Numbers

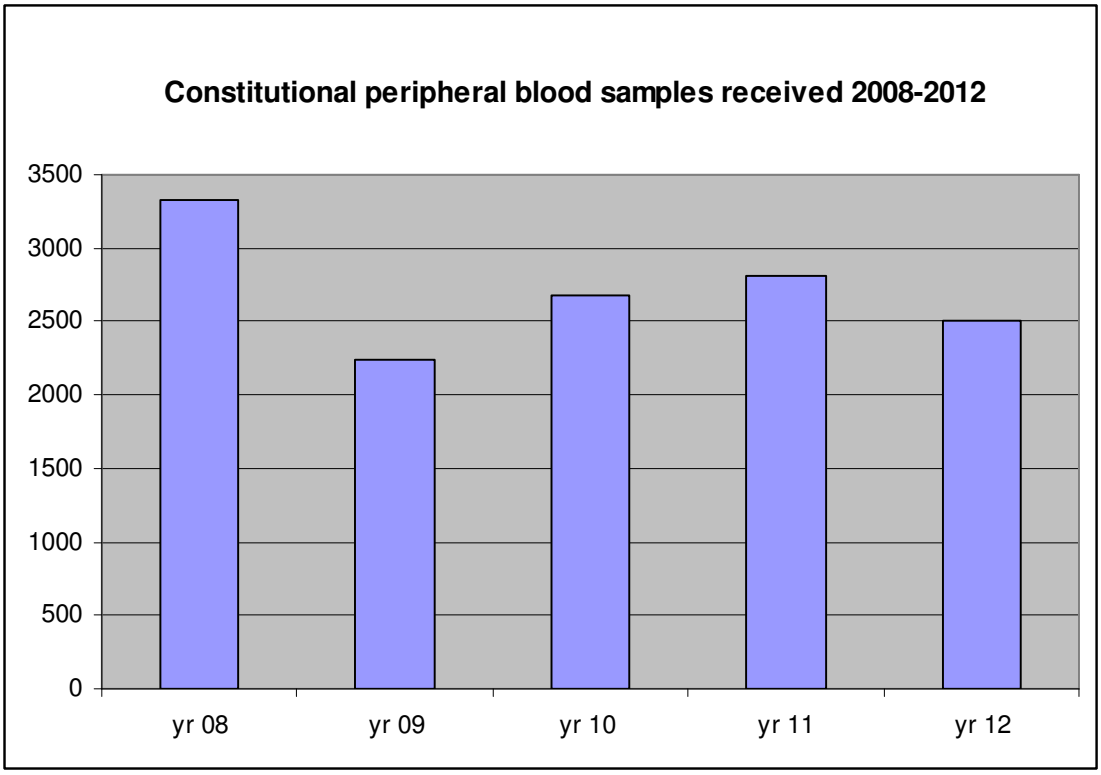
The overall number of samples received in 2012, was fractionally below that of the previous couple of years (see Fig 1). The target set by the Division as being manageable was 6000 samples per annum. This number incorporated an expectation that a microarray service would be available midway through the year and hence, the small decline in 2012 would be expected due to the delay in start and the addition sample numbers that would have resulted from this. As in previous years postnatal karyotyping of peripheral blood samples and bone marrow samples from haematological neoplasms provided the bulk of the Division's work.

Fig 1: Numbers of samples received by the Division of Cytogenetics since 2008 - 2012



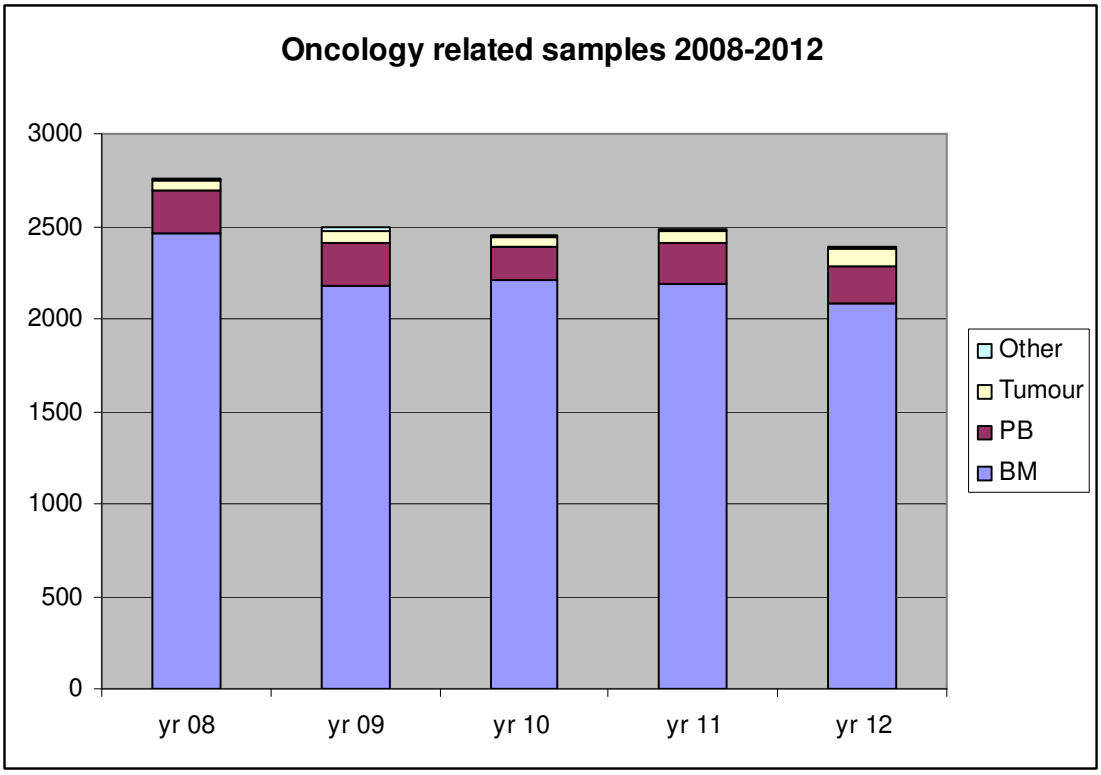
Peripheral blood for constitutional analysis provided the greatest number of samples received by sample type in 2012. There was no change in the acceptance and analysis policy for these samples, but there was an approximate 10% drop compared to 2011 (see Fig. 2). This was almost certainly due to microarray is now the preferentially indicated test for many referral types. It will be expected that this decline continues in 2013 and highlights the need for the Division to be able to offer a microarray service.

Fig 2: Number of PB samples received 2008 – 2012



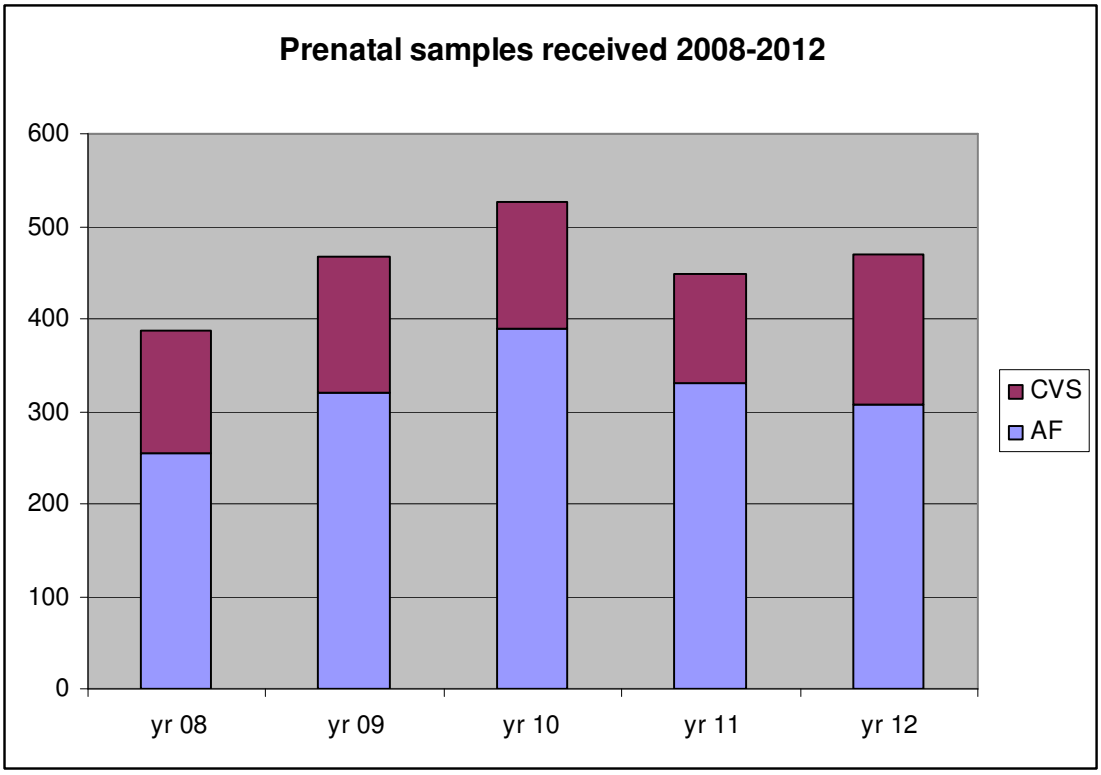
For the haematology/oncology service in there were only minor changes in 2012, but none that affected the actual diagnosis tests offered. The overall sample numbers have remained constant since 2009, and although there was a slight drop in bone marrow numbers 2012 this is balanced by an increase in solid tumour samples (see Fig 3). The number of not required bone marrow samples remains a concern, constituting approximately 45% of all bone marrow samples, and they bring with them an unnecessary work load. In part to address this, it was agreed at an Irish Haematology Society (IHS) in September that we would no longer accept adult NHL bone marrow aspirate samples, but provide a FISH service on bone smears with a confirmed >3% lymphoma involvement.

Fig 3: Number of oncology related samples received 2008 – 2012



A shift in the distribution of amniotic fluid (AF) and a chronic villi samples (CVS) was evident in 2012. Overall there was a small increase in prenatal samples received in 2012 compared to 2011 (see Fig 4), but this was entirely due to a record number of CVS samples. AF samples showed a further drop compared to the peak in 2010. This shift is not without workload implications given the set up requirements for a CVS sample is significantly more time consuming than for AF.

Fig 4: Number of prenatal samples received 2008 – 2012



4.2 FISH

FISH analysis continues to play a major role in the analysis repertoire of the Division, both in terms of stand alone FISH results and supporting the G-band results for both constitutional and oncology samples. Both in 2011 and 2012 major efforts were made to reduce costs by selecting the most cost effective probe supplier while still ensuring quality of the result and reducing the number of repeat hybridisations that were required. There was a small drop in the number of hybridisations performed in 2012, but this was in line with the small drop in overall sample numbers.

4.3 Microarray

The Division went into 2012 with the expectation that an in-house microarray service would be up and running by the middle of 2012. The Division validated and established its own DNA extraction methodology prior to beginning the array validation process. It was planned that there would be a go live date of July 1st, but unfortunately 2 weeks prior to this date, with validation virtually complete, the company supplying the products announced that it was

exiting the array market. A decision was reached to immediately suspend work and begin negotiations with Agilent, who were second in the tender process.

Agilent equipment was installed early October with training and subsequent validation beginning at the end of that month. A redefined go live date of January 1st 2013 was set for OLCHC-related-samples. The Division was able to begin taking NCMG-related samples mid-December for DNA banking and subsequent array post January 1st 2013.

The microarray section took on the DNA banking of peripheral blood for tumour patients in conjunction with OLCHC oncology/pathology departments. It was estimated that there would be approximately 100 samples per annum.

4.4 Accreditation, Quality and Teaching

The laboratory maintained CPA accreditation following a scheduled site visit in spring 2012. However, CPA is pulling out of Ireland and will be replaced by INAB. Hence by the end of 2013 the Division will need to shift to the new accreditation body.

The laboratory continues to participate in all aspects of the UKNEQAS EQA scheme for categories where it current provides a diagnostic service and provides an assessor for the solid tumour scheme. In 2012 the laboratory achieved satisfactory performance in all categories.

During 2012 various staff members of the Division provided teaching both of students and other health professionals, including UCD and TCD students, haematology registrars, and Haematology nursing higher diploma students.

4.5 Outlook for 2013

Whereas 2012 was a holding year 2013 should be a year of change. Microarray will be introduced at the start of the year and bring new dynamic and challenges. The shift from CPA to INAB requires significant work as it is evident that the two bodies have different philosophies and this will require some organisational changes. However, the biggest challenge will be meeting the continuing financial pressure and also the associated staffing levels while maintaining and introducing services.

5 Division of Molecular Genetics

The Division of Molecular Genetic, provides DNA-based testing for inherited disorders to hospital throught the country. 2012 was a particularly difficult year for the Division, with sample numbers soaring by 25%. Since 2009, sample numbers have increased by 85%, while available staff numbers actually declined, placing huge pressure on staff and systems in the Division. The delay (due to external factors) in the introduction of microarray testing in Cytogenetics meant that Molecular Genetics had to continue to provide a send-out service for these tests while the number of requests increased by 40%. The numbers of samples received greatly exceeded the limit which the Division can handle safely, and steps will have to be taken in 2013 to curtail the services offered in order to bring sample numbers back within safe limits. Despite these issues, the Division successfully introduced a service for predictive testing for familial breast and ovarian cancer in September 2012, and many other improvements were made to the service.

5.1 Sample Numbers, Reports & Staff numbers

Sample numbers were up 19% in 2012 compared to 2011, comparing like with like (Table 1). Adding in CF newborn screening, numbers were up 25% to 9,388.

Year	CF NBS	All Others	Total	Reports	Sent Out
2010	-	6187	6187	2410	2905
2011	395	7139	7513	2855	3546
2012	822	8472	9388	2759	4497
Change	108%	19%	25%	4%	27%

Table 1: Molecular Genetics activity in 2012 compared to 2011.

Requests for cystic fibrosis testing were up 16% from 718 to 830, representing the increased family testing following from the introduction of newborn screening in 2011. There was a 76% increase in numbers of requests for breast cancer testing. Requests for Fragile X were down 18% from 927 to 756, most likely reflecting the increase in microarray testing to investigate developmental delay. Microarray requests were up 40% from 1060 to 1487. All of this growth in array requests was from non-NCMG clinicians. Figure 1 shows the changes in sample numbers from 2011 to 2012 by test requested, including CF newborn screening.

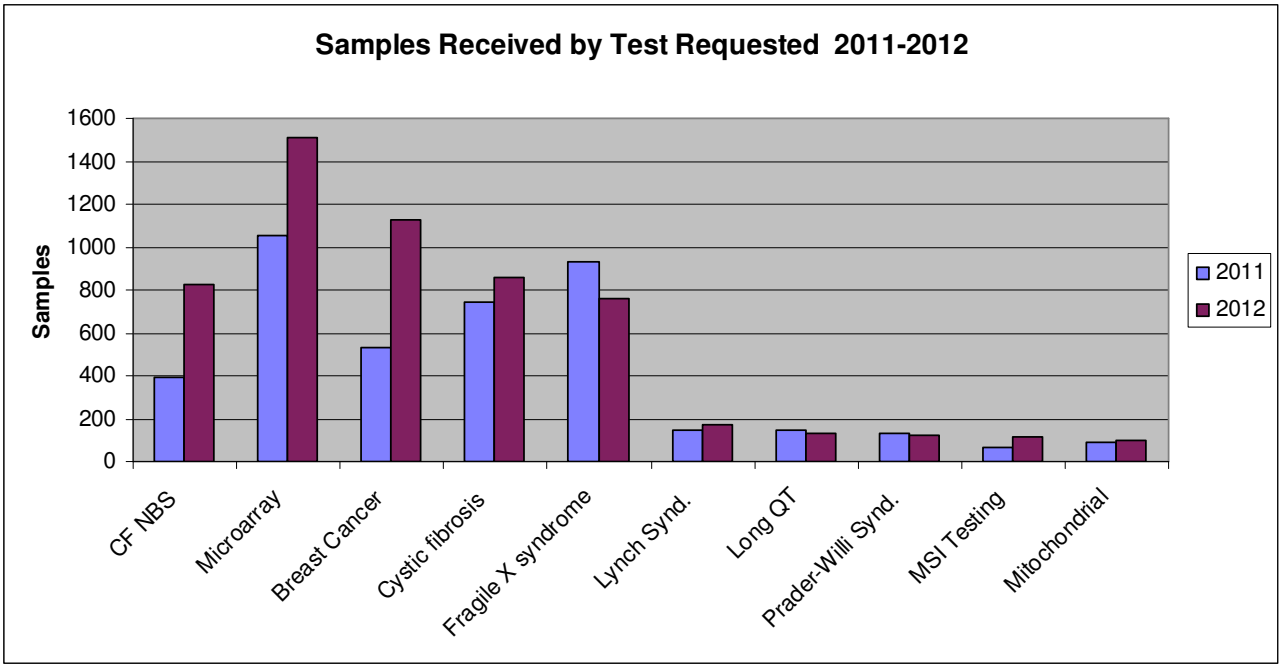


Figure 1: Changes in sample numbers 2011-2012 by disease. Only the 10 most frequently requested tests in 2012 are shown individually.

The figures from the top ten centres sending samples to Molecular Genetics can be seen in Figure 2 below from 2010-2012. In all centres, sample numbers have increased.

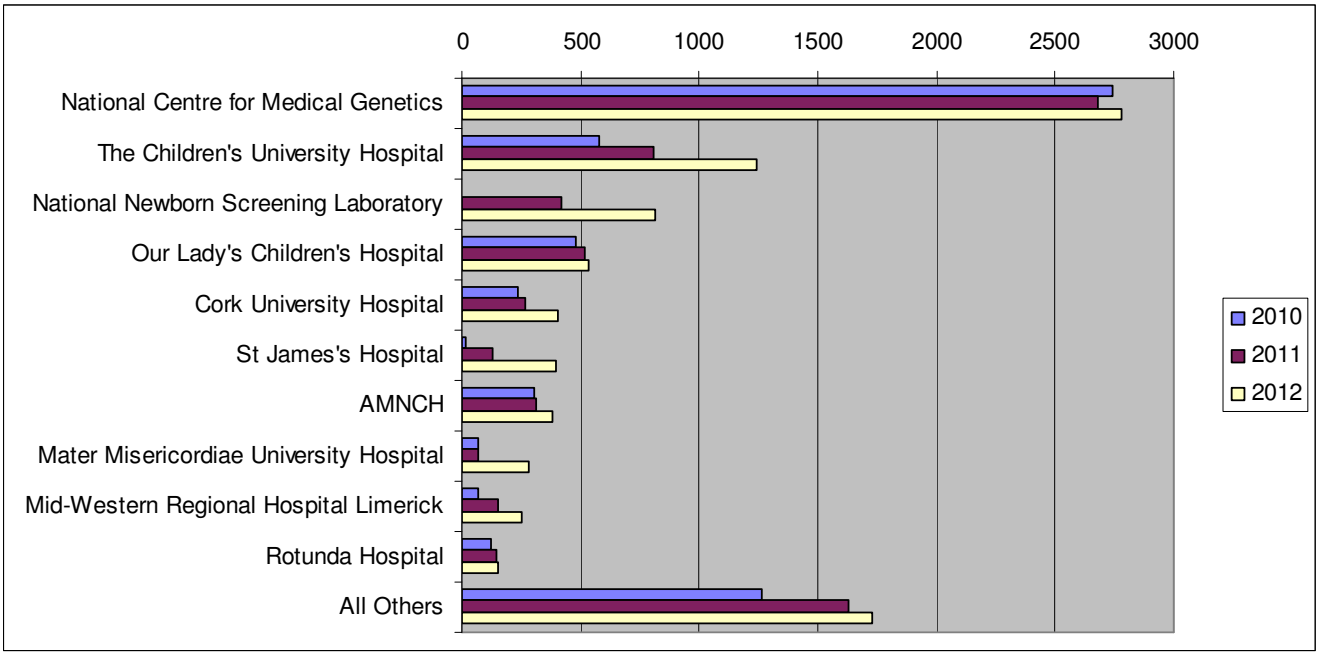


Figure 2: Demand for our service: Analysis 2010-2012. Only the top ten hospitals were selected and all other hospitals are grouped together and called 'All Others'.

Despite the increasing sample numbers, improving the time taken to issue reports (also known as turn-around time or TAT) has been an ongoing objective for all tests. Significant improvements in TATs had been achieved in 2012 in most disorders, and the scope for further improvements without additional resources was limited. The number of reports issued stabilized, with just a 4% increase over 2011. This represented a balance of a decrease in in-house test requests (down 5% overall) and an increase in CF NBS samples. The average reporting time for FRAX tests decreased from 6.8 to 6.2 weeks. Reporting times for Friedreich ataxia and Angelman syndrome were also improved. For the smaller-volume tests, changes in case mix (urgent vs. routine requests) can cause anomalies when comparing average reporting times.

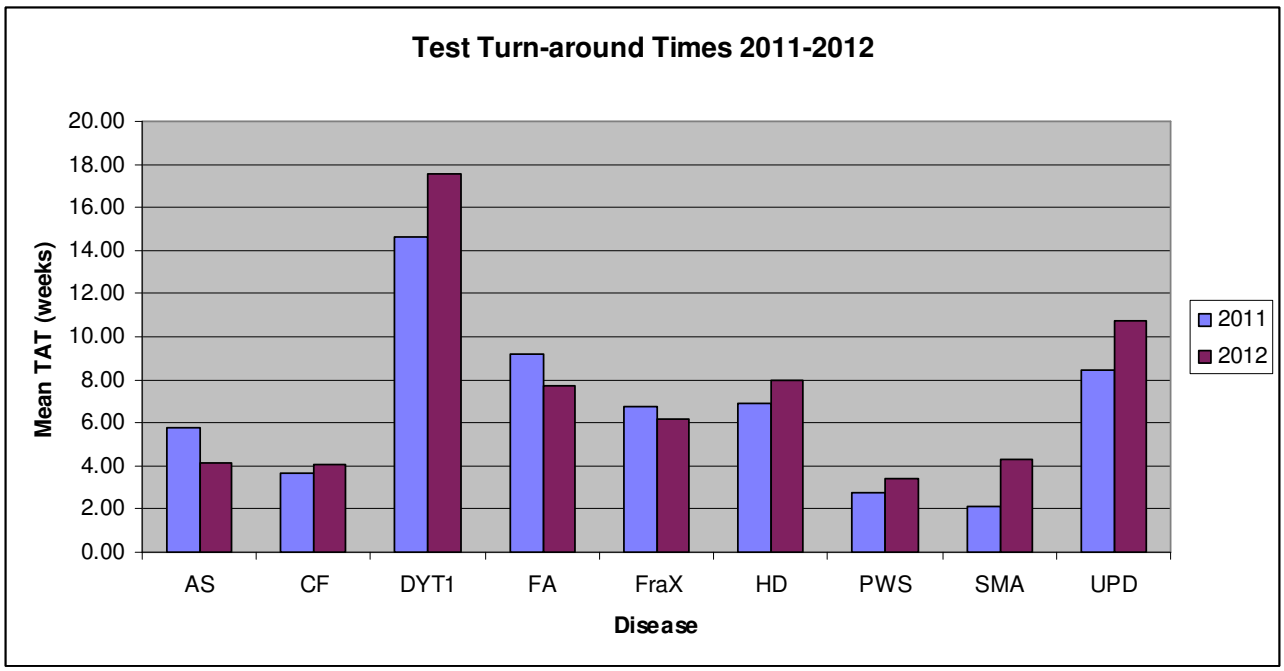


Figure 3: Comparison of reporting times in 2011 and 2012

In addition to the in-house testing, the division prepares DNA & acts as a send-out service for genetic testing to other laboratories worldwide. Sending this work out out has led to a loss of hard-won expertise from the Laboratory, making us very much less of a National Centre. It is certain that these tests could be performed more cheaply in-house, if the money was used to hire staff instead of paying for testing abroad. There has been a steady rise in these sample numbers being sent out with a huge increase in numbers for 2012 (Figure 4).

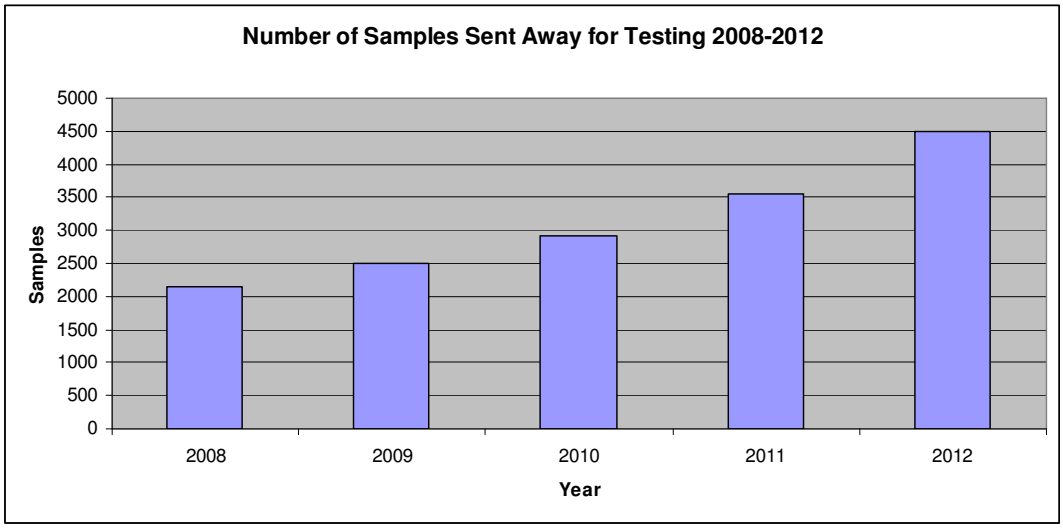


Figure 4: Number of samples sent out for testing from 2008-2012.

In 2011 the number of samples sent away rose 23% in parallel to overall numbers, largely driven by a 51% increase in microarray requests. In 2012, we received 1,500 samples for microarray analysis, a 40% increase on the 2011 figure. Each sample requires processing of paperwork and identity checks, preparation of DNA, packaging and shipping to the testing laboratory and handling of e-mail and telephone enquiries etc. Due to lack of resources & increased sample numbers a decision to potentially stop sending microarray requests is considered for 2013. If this happens, hospitals around the country will have to find their own external provider of microarray testing. This raises iusues of concern regarding the quality of testing, oversight of appropriateness of test requests and fragmentation of information on family members. These issues have been the subject of a clinical safety audit, resulting in the associated risk being listed on the HSE's Risk regiater in 2012. If the Division of Molecular genetics does have to curtail the service of sending away microarray tests in 2013, it will be because an even greater clinical risk (that of errors in the Laboratory) is created by trying to handle these sample numbers while staff numbers continue to decline.

Due to the sustained tight financial position of OLCHC and the moratorium on recruitment and/or replacement of staff, 2012 continued to present challenges for the management and organisation of staff resources. MGM and all Molecular Genetics staff have worked hard together with great team spirit to deal with these changes, to minimise the impact on services and maximise output with decreased numbers of staff. It is a tribute to all staff that so much has been achieved this year despite the ongoing reduction of staff numbers. The situation at Medical Lab Assistant grade continues to give cause for concern, as the increases in sample numbers affect the MLAs most directly. One permanent MLA resigned while on a career break, in December 2012. Our temporary MLA's contract was extended until February 2013. There is little prospect of any additional staff in the foreseeable future, unless the HSE takes up some of our business case proposals. At the end of 2012 the laboratory has an establishment of 22.5 staff (20.46 WTEs) across a range of skill mix.

Our internship programme was further developed during 2012, and formal approval was given by HR for the Division to have 2 interns at a time. Streamlined and closely-monitored training programmes have been developed for the interns, bringing benefits for the laboratory and for the interns themselves. However, these placements are necessarily short-term and therefore impose a heavy training burden on existing staff. The laboratory continues to rely on the help of graduate interns and students on work experience to carry out basic laboratory and office tasks.

The Government, the Health Service Executive, Our Lady's Children's Hospital and the NCMG operate in a financial environment where resources are increasingly scarce, and the medium-term outlook is for this environment to get worse, not better. Much of the time of the Division's Management Group is taken up with juggling staff resources to maintain the service during maternity leave and long-term illness. The HSE's 2012 Service Plan, which envisages a further 7% cut in staff numbers across the HSE, does not indicate that there is any change in this outlook. The effects of HSE moratorium on recruitment include:

- massive pressure on lab office because staff reduced
- knock-on effect on laboratory staff doing admin work
- No replacement for Clinical Scientists on maternity leave – all other CS have to spend more time on rotas, training, reporting duties
- Delay in introduction of new tests
- Hiring of locums/replacements for staff leaving cannot commence, meaning inevitable delays in replacement staff starting, so effects of moratorium will be felt well into 2013.

Demand for molecular genetic testing continues to rise rapidly across all test types and sample numbers continue to increase. Such increases place the laboratory's staff and quality systems under great strain. It is clear that hospitals around the country can find the funds to pay for tests abroad if NCMG cannot do the testing in-house. This creates a clear opportunity to re-direct these funds to NCMG, where the tests can be done more efficiently and all the funds retained in the Irish economy. This could most simply be achieved by allowing the NCMG to charge for the tests it carries out. We have been emphasising this point to the HSE for many years, but it appears that nobody is listening.

5.2 CPA Accreditation

CPA accreditation was granted in June 2010 and the first surveillance visit was held on February 14th 2012. The inspection went very well and the CPA inspector used the words 'fantastic' & 'excellent' to describe our quality management system, management report, EQA performance and records, audits and our CPD & training plans and programs. As a result of this inspection, three non critical NCs and one observation were raised. The Observation that was raised highlighted the current demands on the service in relation to staffing levels. Details of the observation were as follows;

- Staffing currently meets the demands of the service but should be monitored as workload continues to increase. Some services now referred rather than being done in-house to cover maternity leave but no evidence of complaints from users regarding this.

All three NCs were closed and a letter was received in June 2012 confirming continued accredited status for Molecular Genetics. This is a huge achievement for the division and the NCMG and is testament to the hard work and dedication from all the staff in Molecular Genetics.

In early 2012 we received notification from the Executive Manager of CPA (UK) Ltd that, to comply with European legislation, CPA has been forced to withdraw from the Republic of Ireland. Follow up by CPA at the end of the 2012 confirmed that they will continue until the end of 2013 while the transition occurs with INAB and then they will withdraw from Ireland. However, accreditation is still valid, as long as deadlines for submission of documentation are met in the individual department's schedule as with any laboratory enrolled with CPA. This includes submission of an application form and quality manual between April-September 2013. Molecular Genetics will liaise with the Irish National Accreditation Board (INAB) with the prospect of being assessed under ISO 15189 in 2013.

5.3 User Survey

As part of our commitment to improving services at the Molecular Genetics Laboratory, in 2012 we carried out a second user survey with a focus on reporting times. The purpose was to seek the views on the service from our users. The survey was sent to 78 users and only 12 completed surveys were received which is a response rate of 15.4%. We asked our users for improvement suggestions and the following table shows the ideas that were raised by our users along with the reply from us (Table 2 below).

Are there any improvement suggestions you wish to make about the Division of Molecular Genetics	
Idea	**Reply**
When I manage to speak to the scientists they are always very helpful. There can be a difficulty in getting through to a scientist as the phone often reverts to an answer machine. Sometimes it is more than 24 hours before a query left on answer machine is responded to. Perhaps more administrative staff to answer the phones and direct queries appropriately would be useful.	Due to on-going recruitment restrictions we are unable to employ more staff to answer the phones. For all molecular lab queries please contact us by e-mail (duty.scientist@olchc.ie) and a clinical scientist will reply to your e-mail. The e-mail is manned from 9.30-4pm Monday to Friday, so this is the quickest way for you to receive a reply. We aim to reply to all e-mail queries on the day of receipt.
Better PR. Need to advertise your service to avoid DNA samples being sent abroad avoiding safety of going through you	Thank you for your comment. We have made bids to the HSE for additional resources but until these resources are provided we are not in a position to advertise the service more widely. More information about the service can be found on www.genetics.ie
Can we rename it DNA & gene testing please?	We are aware there is some confusion with the type of testing but we are not in a position to change our name at this time. More information about the tests we offer can be

	found on www.genetics.ie or by contacting duty.scientist@olchc.ie
The service is good within the resources limitations.	Thank you for your comment
It would be helpful to be aware of the a) cost of each test as this may play a role whether a test will be requested or b) if the opinion of a clinical genetics is asked for first or c) not requested at all	As we are a national service all our in house tests are free of charge for public hospitals and a full list of these tests can be found on www.genetics.ie We are currently working on updating our website to include a list of the costs involved for any tests we send out to other laboratories. If you require any further costs or testing criteria please contact us on duty.scientist@olchc.ie. We do seek advice from Clinical Genetics if we have any concerns about the appropriateness of a test request.

Table 2: Ideas that were raised in User Survey 20-12 by our users along with a reply from us

Most respondents rated highly the service provided by the Molecular Genetics laboratory with 18% rating the service as 'Excellent', 82% as 'Very Good' and 18% as 'Good', and comments were very positive particularly when it came to the laboratory staff. Greater than 97% of respondents rated the quality of advice or information received from the staff of the Molecular Genetics Laboratory as excellent or good. Some of the comments are as follows:

- Find staff very helpful in difficult circumstances.
- Service is very good.
- Staff friendly and courteous and very much clinically driven and helpful.

As the staff are the single most important asset in the laboratory it is great to see that these comments from users reflect the great work from all staff in Molecular Genetics.

5.4 External quality assessment (EQA) reports

The Division of Molecular Genetics participated in the following EQA schemes in 2011:

- *United Kingdom National External Quality Assessment Scheme (UKNEQAS) for Molecular Genetics*
- *European Molecular Genetics Quality Network (EMQN)*
- *Cystic Fibrosis (CF) European Network*

For 2011-2012 the Division of Molecular Genetics participated in ten UKNEQAS, five EMQN and one CF European Network schemes. This was a total of 16 schemes, 51 genotypes and 42 fully interpreted reports. A summary of the participation and performance in these EQA schemes are given in DOC1836. These schemes cover a majority of the aspects (domains) of the services offered by the laboratory. As performance was near perfect and other demands on the service were very high, feedback meetings were not held in 2012.

A perfect score of 2.00 for genotyping and a mean score of 1.96 for interpretation was attained for the diseases/techniques CF, DNA-Seq (Full), DMD, FraX (full), FRDA, HD and PWS/AS in the EMQN (including the CF Network) EQA schemes. A perfect score of 2.00 for genotyping and clerical accuracy and a mean score of 1.94 for interpretation was attained for the diseases CF, CF-DBS, DMD/BMD, FraX, FRDA HD, MCC, MSI (pilot scheme), PWS/AS and SMA in the UKNEQAS EQA scheme. The Laboratory performs extremely well in these UK and European EQA schemes, consistently ranking in the top 10% of laboratories with similar test repertoires.

No adverse NCs were raised for the 2011 EQA schemes. There were only two incidents of loss of 0.5 marks and 0.25 marks, respectively (of a total of 222 marks), for interpretation in the UKNEQAS SMA and EMQN FraX schemes. This resulted in a non-adverse NC being raised for SMA and a reporting policy change for new Bayes scenarios (INC763). The loss of marks for the FraX scheme (INC929) was appealed as we did not agree with the deduction, for an interpretative point. The appeal was not upheld, but we do not agree with the assessment and no further action is required.

From previous EQA feedback meetings, the need for a 'laboratory wide' consistent generic report format was identified. A new (colour coded) reporting template was agreed (DOC1488) and was phased into use for all reports during 2012.

These consistently excellent EQA results are testament to the hard work, skilled expertise and commitment to quality that is shown by the staff of the Division of Molecular Genetics, and is particularly commendable in the current challenging environment.

5.5 Training & Education in Molecular Genetics

All training and education issues are discussed at the MGM and diagnostic meetings and minutes are available. No separate training and education committee meetings were held in 2012. The Training budget for 2012 was cut by 5% in line with the Centre's budget, leaving €5,700 for the whole centre, divided equally between the three Divisions i.e. €1900 per Division. Although an additional €2,000 became available with funding for the cystic fibrosis newborn screening programme, this limited budget continues to restrict training and continual professional development (CPD) activities. The Division of Molecular Genetics continues to try to maximise on dissemination of information from attendance at courses and conferences. Reporting back takes place at the first Diagnostic meeting after the course/conference, via a short written report circulated by email or through another appropriate forum. All supporting documentation in centrally located electronically at dnalab:\Course & Conference Feedback. The Division also continues to source and access as many free resources as possible to advance CPD, including desktop conference facilities. The Division introduced its own CPD points system which was fully implemented in 2012. This system will help evaluate the amount and content of individual CPD activity and highlight

any deficits that may be contributed to by lack of funding. Formal training programmes for each staff grade continued to be developed throughout 2012 and also applied successfully to the internship programme. Competence assessments continued to be rolled out in 2012 but increasing workloads have impeded progress especially in the area of compilation of reference data for technical competence assessment. MGM will examine ways to assist this in early 2013. Also in 2013, a review of the roles of Training Team members is planned in view of diminishing staff resources. A review of the training structure for Refresher Training is also planned and from this, a structure for Intern/all staff observations ('shadowing') will be put in place. Again, because of diminishing staff and funding resources, a review of the Education structure and its overlap with Training is warranted. All of these plans been included in the 2013 objectives.

5.6 Molecular Genetics changes in service in 2012

Cystic Fibrosis Newborn Screening (NBS)

CF Newborn Screening, which is carried out in conjunction with the national newborn screening programme for inherited metabolic and genetic disorders, based at the Children's University Hospital, Temple Street, Dublin, began on 1st of July 2011. The NCMG receives a dried blood spot sample on the top 1% of newborns found to have an elevated IRT result. As of 31st December 2012 (18 months), 109,764 newborns have been assessed for elevated IRT as part of the national newborn screening programme and 1,207 have been referred to the NCMG for DNA analysis. Of these 1207 patients, thus far 38 patients have been found to have 2 mutations following our initial analysis. A diagnosis of CF for these patients is confirmed following a sweat chloride result of >60mmol/L. A further 93 patients have been found to have 1 CF mutation following initial analysis. 86/93 were confirmed as carriers only with a sweat chloride result in the normal range. 4/93 were found to have positive sweat tests thus confirming them as having CF and a further two cases were found to have borderline sweat tests requiring further investigation. Full screening of the CFTR gene is then carried out on positive and borderline sweat test cases to identify if a second CF mutation is present. The assay employed to analyse all the CF NBS samples, as well as all routine CF samples received to the NCMG, is the Luminex xTAG CF39 assay which tests for 39 CF mutations and 4 variants. The 39 mutations include the 23 mutations that are currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynaecologists (ACMG/ACOG) and 16 of the worlds most common CFTR mutations. The use of this assay allows for the detection of ~93.5% of CF mutations seen in the Irish population.

Fragile X service and a new assay

The introduction of the Amplidex assay (Asuragen Inc.) in 2011, which allows the detection of all classes of FMR1 alleles, including full mutations, resulted in the cessation of Southern blotting with radioactive DNA probes. This change over allowed the decommissioning of the radiation room in 2012 and room's conversion to a DNA preparation area.

The in-house FRAXA PCR assay based on O'Connell et al., 2002, and ABI sizing of fmr1 alleles on the ABI 3130xl continues to be the primary screen, with a minority of patients' samples 'reflexed' to the Amplidex assay. The Amplidex assay was successfully validated for prenatal samples and three Fragile X prenatals were performed in 2012 with the assay, which substantially reduced the reporting turn-around-time.

In 2012, the number of query affected referrals decreased by 23.5% compared to the previous year, whilst the number of all Fragile X referrals decreased by 18.5% compared to 2011. This most likely reflects a shift towards microarray analysis as the first line of investigation in developmental delay.

Duchenne Muscular Dystrophy and Spinal Muscular Atrophy services – resumption of SMA and continued cessation of DMD

Due to the concurrent maternity leaves of three very experienced clinical scientists (including one Principal) in Q3 of 2011, two of which were the lead reporting / checking scientists for Duchenne Muscular Dystrophy (DMD) and Spinal Muscular atrophy (SMA), a decision was made to temporarily cease in-house testing for DMD and SMA. A major contributory factor was the imminent implementation of the CF NBS service also in Q3 of 2011, as the third scientist was a lead reporting / checking CF scientist. It was decided that there simply wasn't sufficient clinical scientist resources to sustain DMD/SMA testing and introduce the CF NBS scheme. Training of a GT for SMA was completed in 2011 and the SMA service was resumed in Q1 of 2012. Unfortunately, due to the subsequent long term illness post maternity leave (until Q4 of 2012) of two of the experienced clinical scientists, there were insufficient staff resources to enable the resumption of the DMD service. MGM will assess whether or not the DMD service will resume in 2013 as part of the overall service objectives for the year.

Lynch Syndrome / Microsatellite Instability (MSI) service changes and service resumption.

Since the re-introduction of microsatellite instability (MSI) testing for the investigation of Lynch syndrome (previously known as HNPCC) in 2008, the Histopathology laboratories of Our Lady's Children's hospital provided IHC testing for the MMR proteins involved in Lynch syndrome. Part of this process was also to cut and prepare slide sections from patient tumours for subsequent DNA extraction and MSI analysis.

Unfortunately, the Histopathology lab had to cease the provision of this service in early 2011, and the service was outsourced to an adult hospital in Dublin mid 2011. However, this laboratory did not wish/have the resources to prepare slides for DNA extraction/MSI analysis, and another adult hospital in Dublin (St James's) was approached late in 2011 to provide this service. MSI testing had to be temporarily suspended, but resumed again early 2012 once service level agreements were put in place. The Lynch Team worked diligently throughout 2012 to liaise with both our Clinical Genetics Team and St James's Histopathology Team to establish new sample pathways to make the system more effective and user responsive.

Concurrently, the Lynch Team introduced and validated the Advanced EZ1 robot for FFPE DNA extractions and the commercial Promega MSI kit to streamline the previously very labour intensive MSI testing. A new BRAF assay was also developed to compliment the pre-screen workup of Lynch Syndrome. These service developments will be completed in 2013 (objective 2013) and will result in a more efficient testing pathway and much decreased turn around times.

BRCA predictive testing

A BRCA predictive service for sequence-based pathogenic mutations in BRCA1 and BRCA2 was implemented in-house from the start of September 2012. Prior to this, all predictive tests were performed by an external laboratory at a cost of £223 per test. Prior to implementation a verification process was performed during Q1,Q2 & Q3 that involved the blind testing of all samples received for a sequencing analysis-based predictive BRCA from July – December 2011. Mutation Surveyor analysis of sequencing data was an integral part of this verification process. Primer sequences used for BRCA full screening and predictive testing by the West Midlands Regional Genetics Laboratory, Birmingham were provided for use in the NCMG service and staff from that lab were very helpful during the implementation stages. An important part of the verification process involved a survey to other BRCA testing labs to obtain information on their policies for dealing with SNPs within primer sequence regions, and analysis in the absence of a mutation positive control from a family member. Results from this survey were then used to form a basis for the development of policies and procedures for the NCMG service. Results are reported using fixed report templates that were developed in collaboration with the NCMG Clinical Genetics team. It is envisaged that this report template system will facilitate the move towards report generation by genetic technologists in addition to clinical scientists. In conclusion, the scope of the in-house BRCA predictive service is analysis of sequence-based pathogenic mutations for which there is a mutation positive control available. If the mutation is one that requires MLPA, or one for which there is no positive control in-house, the sample is sent to an external lab for analysis. Since the implementation of testing in-house at the start of September 2012 to the end of

December 2012, in-house reports were issued for 86 predictive tests and 29 tests were sent to external labs due to the requirement for MLPA analysis or due to the unavailability of mutation positive control. The turnaround time for in-house analysis is 4-6 weeks (28-42 days) and this was obtained for 88% of samples (Christmas break included) or 98% of samples (Christmas break excluded).

5.6.1 Prenatal diagnostic service

The number of prenatal samples for molecular genetic testing continues to increase year on year. There was a 40% increase in 2012 in the number of prenatal samples received compared to the previous year (see table 3). The year on year increase in PND samples received was 39% and 48% for in-house requests and send-out requests respectively. The overall number of PND notifications (cancelled PNDs and PND samples received) increased by 19% in 2012 compared to 2011.

Year	CVS	Cultured CVS received	Cultured amnios received	Direct amnios received	PND samples received	PND notifications	Cancelled PNDs
2011	**32**	**4**	**11**	**0**	**47**	**67**	**20**
2012	**47**	**7**	**9**	**3**	**66**	**80**	**14**
Increase	*47%*	*75%*	*-18%*	*300%*	*40%*	**19%**	**-30%**

Table 3: Number of PND samples & notifications received for 2011 & 2012

Year	In-house PND tests performed	In-house request not tested (banked)	External tests (send-outs)
2011	**18**	**4**	**25**
2012	**25**	**4**	**37**
Increase	*39%*	*0%*	*48%*

Table 4: Number of in-house & external PND tests for 2011 & 2012

The number of maternal blood samples received for non-invasive foetal sex determination (cell-free foetal sexing from maternal plasma), which are sent out directly to the U.K., increased by 60% (n=16 in 2012; n=10 in 2011). The majority of these cell-free foetal sexing requests are for X-linked disorders and the detection of a female foetus reduces the need for PND in these families.

Future plans include the employment of the semi-robotic EZ1 system for the efficient extraction of DNA from cultured amnios and CVSs. The implementation of this protocol will substantially reduce the number of phenol/chlorofom DNA extractions, which are time-consuming & technically more difficult to perform. MLA staff will be trained in the Promega Powerplex PCR assay employed in determining maternal cell contamination in PND samples. However, all developmental plans for the molecular genetics PND service are dependent on staffing resources and budgetary constraints.

5.6.2 DNA Preparation

An ongoing project to validate both of the EZ1 Biorobots for the preparation of DNA from chorionic villus prenatal samples for all in-house testing was completed in 2012 (DOC1995). This introduction reduces the need for the use of the hazardous chemical phenol and substantially decreases the process time for these time sensitive samples. External laboratories providing PND testing were also able to accept EZ1 purified CVS DNA for their analysis, so now all direct CVS samples are prepared in this more automatic fashion. A decision was made not to continue with the validation of the EZ1 robots for cultured CVS and amniocyte cells as these sample numbers are very small, the DNA yields are variable and there is a need to maintain stocks of, and competence for, phenol extractions of small sized direct chorionic villus samples.

Tissue extractions were also validated on both EZ1 platforms in 2012 (DOC2001) and there is some more minor work and/or documentation required to complete the verification of all bloods and dried blood spots on both machines (objective 2013). Formalin fixed paraffin embedded (FFPE) samples such as slide preparations from tumour blocks were also validated on the Advanced EZ1 robot. This DNA extraction method complimented the introduction of the more efficient Promega kit for Microsatellite Instability (MSI) and a new BRAF assay analysis for Lynch Syndrome. This work is almost completed and is due to be finished in 2013 (objective 2013).

Due to the sustained growth in sample numbers throughout 2012, an increasing number of DNA extractions were moved from the manual Puregene method to the EZ1 robots to allow the service more safely manage the workload.

There is an ongoing requirement for a higher-throughput DNA preparation instrument; it is unlikely that the laboratory can expand its services or deal with the year on year sample increases and complexity (see section 3.2.2, activity levels) while relying on the current mix of small-scale EZ1 extractions and labour intensive manual protocols.

5.6.3 Genetic & Rare Disorders Organisation (GRDO)

The NCMG, represented by Prof David Barton, continued its close interactions with an alliance of stakeholders representing patients and others affected by rare diseases. Prof

Barton was invited to speak at the European Conference on Rare Diseases in Brussels in May, delivering talks on "Molecular Diagnostics in Real Life" and "The Regulation of *in vitro* Diagnostic Devices".

Work continued on the development of a national rare diseases plan, as required of the Irish government under the European Council Recommendation on European Action in the field of Rare Diseases of June 9, 2009. A steering group has been set up for this purpose at the Department of Health. NCMG staff (Prof Barton, Dr Lynch, Ms Rose Kelly) are actively involved in the broader Rare Diseases Task Force which provides input to the Steering Group.

5.7 Molecular Genetics plans for 2012 & onwards

5.7.1 Service planning & implementation of copy-number variation analysis

The NCMG planning group with responsibility for the implementation of copy-number variation 'array' analysis was successful in sourcing funding from the Children's Medical Research Foundation in mid 2010. The Division of Molecular Genetics collaborated with the Division of Cytogenetics in 2011 to complete the tender process and place an order for the Roche Nimblegen platform. Training for DNA extraction was completed with a Clinical Scientist from Cytogenetics in early 2012. There was close liaison between Molecular Genetics and the Cytogenetics array team to provide previous extracted DNAs and duplicate bloods for the validation of the instrument, with the intention to 'go live' on the 1st July. Unfortunately, without notice, Roche pulled out of the array market and the entire process of instrument acquisition and validation had to be re-started. Financial compensation was actively sought and obtained. It is now planned to offer array testing from the beginning of 2013 using the Agilent platform. All Divisions of NCMG will continue to liaise to implement sample pathways for the diagnosis of children with intellectual disability in 2013.

5.7.2 Service planning & implantation of Next Generation Sequencing

New genetic technologies are revolutionising medicine. Recent advances in next generation sequencing (NGS) technologies have brought about a paradigm change in how medical researchers investigate human disease. These transforming technologies are now bringing a major shift in clinical practice in terms of the diagnosis and understanding of genetic disorders. NGS is set to change medical genetics and the diagnosis of genetic disease in the same way that mobile phones and the internet have revolutionised global communication and information systems.

NGS permits the study of mutations and their role in disease in a systematic genome wide (global) manner, in comparison to previous sequencing methods that could only look at one very small part of one gene at a time. It is now being used in clinical diagnostics for the

accurate, rapid and cost-effective identification of changes in targeted genes e.g. CF & BRCA1/2. It is also being applied to target 'gene packages' (e.g. cardiomyopathies, sensory disorders, neuropathies and muscular dystrophies) and 'whole exome sequencing' – such as for children with learning disabilities or mental retardation, where the entire coding DNA of all known genes was sequenced and *de novo* mutations identified.

The Division of Molecular Genetics recognises the need to acquire and introduce this technology into the service, and has incorporated this into the Business plan submitted to the HSE (March 2011, see section 3.4). The business strategy is to use this high through put, massively parallel sequencing technology to test more cheaply in-house for the diseases that are currently sent out (at a very significant cost ~€500,000 in 2011). NCMG management also supports this approach. MGM's approach to acquiring funding and implementing NGS during 2012 was two-fold.

Firstly, Roche Applied Sciences had placed (for free, late 2011) a bench top NGS platform in the laboratory which afforded the opportunity for a group of clinical scientists, genetic technologists and a post doctoral researcher to receive training and try out this new technology first hand. Members of this group also investigated some of the commercial bioinformatics software available to process and detect the pathological changes in the patient samples tested. MGM submitted a proposal to the Hospital mid 2012 to fund the consumables to validate this specific technology and the commercial software to analyse the results, but the proposal was not successful due to financial constraints. Further attempts to procure validation funding were not pursued as the running costs of the Roche system were expensive and labour intensive in comparison to cheaper to run systems that were becoming available on the market. Secondly, and with this in mind, MGM submitted a detailed business proposal to the Hospital's Medical Equipment Procurement Committee to acquire a higher throughput (and therefore more cost efficient) NGS platform and set up costs. The latter included validation consumables, analysis software, robotics and a 12 month temporary clinical scientist's salary to implement this new technology.

In October 2012, recommendations were made for the purchase of an NGS system, pending availability of funding. Unfortunately, by year end, the NCMG's expenditure was significantly overrun, so the likelihood of funding becoming available for a NGS system in 2013 is slim. Also, the Hospital was not in a position to fund the temporary staff member to implement the technology. The Committee suggested that we enquire about the possibility of the Children's Medical Research Foundation funding same. This possibility is being investigated. MGM will continue to explore as diligently as possible, the means to establish this technology to expand and future proof the service we offer to our patients, users and the people of Ireland (objective 2013).

6 Administration

6.1 Relationship to the host organisation

The NCMG is located on the site of OLCHC. Funding allocated to NCMG is currently administered by OLCHC. The relationship with the host organisation is shown below (Fig 1):

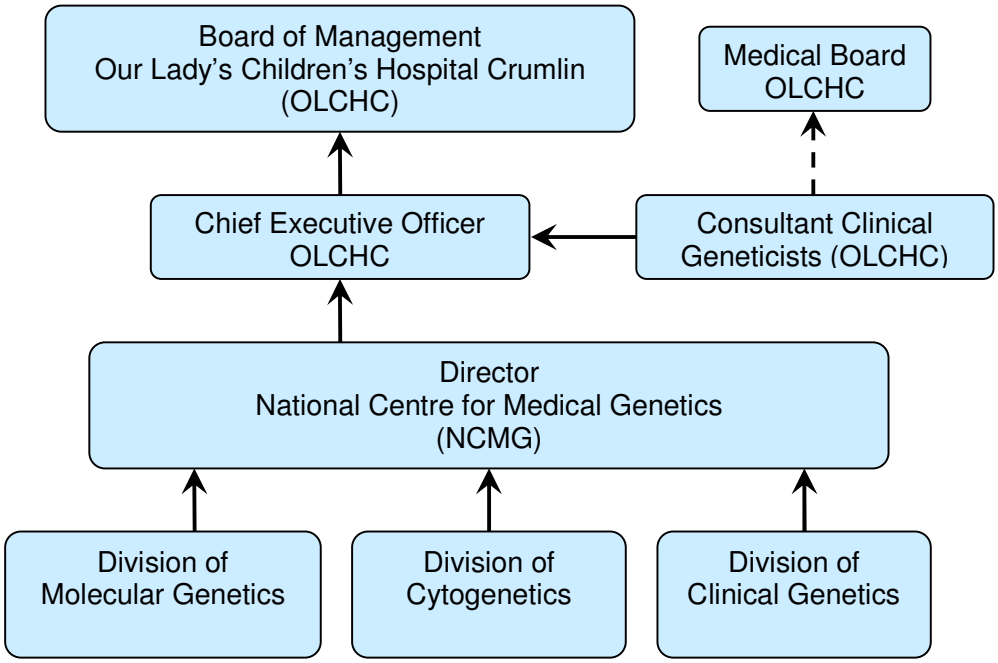


Fig. 1 Relationship of the NCMG within OLCHC.

6.2 Organisation and responsibilities within OLCHC

OLCHC is an acute paediatric teaching hospital with 248 beds, employing over 1,500 staff. It is Ireland's largest paediatric hospital and is responsible for the provision of the majority of tertiary care service for children including the National Centres for Paediatric Surgery, Haematology/Oncology, Major Burns, and Medical Genetics. The hospital also houses the world renowned Children's Medical Research Centre. The Hospital is governed by a Board of Directors, Chaired by His Grace, The Most Reverend Diarmuid Martin, Archbishop of Dublin. Mr Lorcan Birthistle is the Chief Executive Officer.

There is good cooperation between OLCHC departments and participation in committees where appropriate. The OLCHC Health & Safety Committee meets monthly. Its membership

consists of OLCHC management and two staff representatives, elected by the OLCHC Health & Safety Forum. The OLCHC Health & Safety Forum meets quarterly. OLCHC encourages the appointment of staff Safety representatives as specified under section 25 of the Safety, Health and Welfare at Work Act 2005. The role and functions of the Safety Forum is distinct from that of the OLCHC Health & Safety Committee, and they compliment each other. The Forum's membership consists of staff representatives from various departments throughout the hospital, including the NCMG. The Forum elects two of its members to the Hospital Health & Safety Committee.

6.3 Organisation and responsibilities within OLCHC

The NCMG is under the directorship of a Consultant Clinical Geneticist and Professor of Medical Genetics at University College Dublin (UCD) who is responsible to the Chief Executive Officer (CEO) of OLCHC for the management of the service, see section 3, General Information.

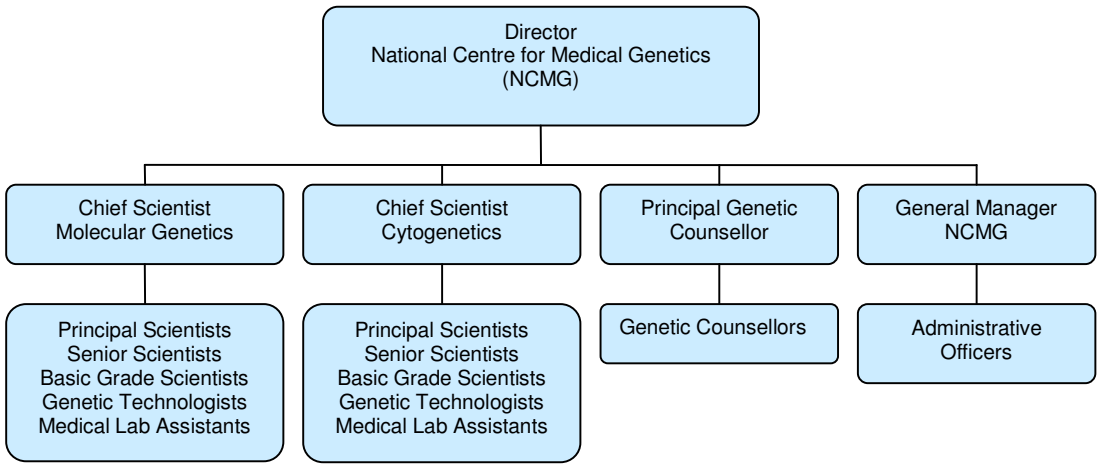


Fig. 2. Organisation within the NCMG.

The **NCMG Management Team** is an inter-divisional committee representing diagnostic, administrative, clinical and research (University College Dublin (UCD)) within the NCMG. The group meets once a month. Minutes are disseminated and updates from the NCMG management team are held with all NCMG staff once a year or when required. Its membership is as follows:

- Director
- General Manager

- Head of Molecular Genetics
- Principal Molecular Genetics Scientist
- Head of Cytogenetics
- Principal Cytogenetics Scientist
- Consultant Clinical Geneticist
- Principal Genetic Counsellor
- Research Representative (UCD)
- Administrative Officer Representative

The **NCMG Health and Safety Committee** meets as required. Its membership consists of:

- Molecular Genetics Health & Safety Coordinator
- Cytogenetics Health & Safety Representative x2 (also departmental H&S reps for OLCHC)

The **Specimen Reception Committee** meets as required. Meetings are attended by staff from the division of Molecular Genetics and Cytogenetics. Minutes of all meetings are prepared and circulated and are available to all members of staff on a shared NCMG network drive.

Other groups & committees are formed and meet on an 'ad hoc' basis as required to discuss shared items.

6.3 Administrative Team

The administrative support team at NCMG provides essential support to all three divisions and are an integral part of the centre as a whole. As of the end of 2012 there were 7.97 WTE administrative staff in NCMG – this was divided between the Clinical, Molecular and Cytogenetics divisions. In terms of administration, the NCMG operates as a standalone administrative service within OLCHC and is not part of the wider hospital admin pool for cover or staff redistribution. We do not use the hospital clinical or laboratory booking systems, instead all clinical appointments are booked and sent directly from NCMG and all laboratory referrals are booked and processed on the respective Molecular Genetics and Cytogenetics databases. Clinical administrative staff assist with triage, set up patients on our specialised database system, create family medical records before booking appointments, and type and send clinical letters. Administrative staff are primarily the first point of phone contact for both families and clinicians. As a national centre they also deal with a high volume of general enquires. They oversee the administration section in the laboratory from booking in samples on two laboratory databases to the issuing and posting of reports. They

deal with telephone enquiries regarding results of tests and the payment of invoices for tests sent abroad (approximately 3,000 per year).

The NCMG store all our patient records for the clinical division on site and currently have over 20,000 patient records. Our charts are family based, as opposed to individual charts, and the charts are for both children and adults, and as such are stored separately in NCMG and not in the main OLCHC filing room.

The Government and HSE public sector staff embargo continues to have a significant impact on our administrative staffing numbers. As of the end of 2012 the administrative staffing numbers were 24% below their original approved numbers. The administrative team continues to adapt its service and seek efficiencies to minimise impact for patients and the service.

7 Engagement with OLCHC, HSE & DoH

Mr Lorcan Birthistle visited the NCMG, as part of a series of department visits throughout the hospital, on the 18th April 2012. Mr Birthistle met with members of the NCMG management team. A pre-requisit as part of the CPA Post Accreditation Assessment is for laboratories to meet with the chief executive of their institution. The three divisions of NCMG therefore presented the CEO an update post-accreditation on current work and the challenges facing the service.

We met with Dr Susan O'Reilly and the National Cancer Control programme on 19th January and 28th May.

The Dept of Health rare disease meeting was held on 11th June, in Farmleigh, attended by several NCMG staff members.

Submissions to the HSE

Document title	Authors	Recipient	Date
Addressing hereditary breast cancer clinical assessment & gene testing in Ireland	AJ Green, DE Barton & D Moyles	Susan O'Reilly NCCP HSE	May 2012
Template for escalation of risks to next level governance Structure	SA Lynch & AM Kiernan	Annette Macken & Dr Phlip Crowley HSE	July 2012
Letters requesting workforce planning	SA Lynch & AJ Green	Eilis McGovern, MetB unit HSE	June & Dec 2012
Letter requesting workforce planning	SA Lynch & AJ Green	John Magner RCPI	July 2012

8 Teaching

- Dr David Barton Participated in teaching a course on "Quality Improvement in Genetic Testing" in India and Sri Lanka, February 2012.
- Dr Sally AnnLynch gave
  - two talks to UCD medical students participating in the Rare disease module in March 2012
  - a talk to the paediatric SpRs on the 16th November 2012
  - a talk to a group of Psychiatrists (who work in the field of learning disability) on the 30th November 2012

9 NCMG Committee Representation

Members of the NCMG serve on a range of Local, National, European and International committees, councils and working groups as out-lined below.

Name	Committee	Dates served
David Barton	Management Committee, European Molecular Genetics Quality Network	1998 - present Chair 2011
David Barton	Steering Committee EuroGentest Network	2011 - 2012
David Barton	Genetics Services Quality Committee, European Society of Human Genetics	2010 - present
Caitriona King	Irish Society for Human Genetics (ISHG) Council	2007 - present
Sally A Lynch	Republic of Ireland on Specialist Advisory Committee UK	2009 - present
Andrew Green	Chair of the research ethics committee & research forum OLCHC	2006-present
Andrew Green	Health Service Executive research ethics advisory group	2011-present
Andrew Green	UCD research ethics committee - member	2004-present
Andrew Green	UCC review committee on embryonic stem cell research [chair of group since 2010]	2006-present
Andrew Green	Chair of the Department of Health Advisory Committee on Bioethics	2011-present
Andrew Green	Advisory Council for EUROCAT – European congenital anomaly register	2002-present
Debby Lambert	Health and Social Care Professionals on the Ethics Committee Temple Street	2007-present
Nicola Harper	Sudden Cardiac Death Resource committee.	2011-present
Marie Meany	AGNC representative for NCMG	2007-present
Rosemarie Kelly	Rare disease taskforce	2011-present
Caitriona King	Irish Society for Human Genetics (ISHG) Council	2007 - 2012

10 Research

10.1 The Genetics of Vesicoureteric Reflux

The disorder

Primary vesicoureteric reflux (VUR), the retrograde flow of urine from the bladder towards the kidneys, is the commonest urological anomaly in childhood and occurs in 30-40 % of children who present with urinary tract infections. Some of these children have congenital renal dysplasia, and renal damage may also develop due to reflux of infected urine. These problems are jointly known as reflux nephropathy, which is a major cause of childhood hypertension and end stage renal failure. The incidence of VUR is unknown because it is often asymptomatic and often resolves as the child grows, and screening is not ethical or practical because diagnosis requires invasive investigation. Estimates vary between about 1 & 10 %.

The genetic problem

VUR is frequently familial and is often associated with other congenital anomalies of the kidney and urinary tract (CAKUT) in the same individual or in other members of the same family. Screening is offered for siblings of diagnosed children, and often reveals asymptomatic children, but screening may be refused if the children are symptomless, and even if screened, reflux may already have resolved though a mutation may have been inherited. Because the phenotype is not obvious, collecting large pedigrees is difficult. Added to these problems, it has become increasingly evident during the course of this project that VUR is highly genetically heterogeneous. This means not only that many different families in the same study are likely to have mutations in different genes, but also, because VUR is common, in large pedigrees, different affected cases may not have the same mutation. Furthermore, it has emerged recently that some mutations may require a second mutation in the same or a different gene to produce the phenotype.

The project

The aim is to discover the genes and mutations responsible for VUR. Recruitment of VUR families and collection of samples for DNA has been ongoing here since 1998. There are at least 12 other centres worldwide working on the problem, and this is enlarged if one includes groups concentrating on obstructive uropathy, on renal dysplasia, or on CAKUT in general, all of which have overlapping aetiologies. We are working largely on our own, but attend meetings of investigators in the field, and have arranged collaborations on specific investigations with workers in Paris, Manchester and Melbourne, as well as having data and sample sharing agreements with groups in the UK (Newcastle & London), New York and Montreal. We had collected 250 families by the end of 2011, and are grateful for the use of 592

Irish blood-donor control DNA samples from the TCD-Trinity BioBank, and Affymetrix 6.0 SNP array genotyping data from around 850 of the BioBank samples. Technology is advancing so rapidly that it tends to become obsolete soon after it is introduced, and this has played a considerable part in moulding the course of our own investigations.

Personnel

John Darlow
Mark Dobson
Interns: Caitríona O'Brien and Luke Gubbins till early March. Michael Vogl (intern from June – September) also did a little work on our project).
Students: Goh Ser Wei, Caroline and Phua Ler Yee, Valencia, March-June.

Summary of work during 2012

1. Reanalysis of data of the new genome-wide linkage, association and copy-number scan started in 2010 (Item 4 of the summary of work in 2007-2011), and preparation for publication of the linkage and association results. This was a very large project and work continued on it all year. Caitríona O'Brien carried out PowerPlex (DNA fingerprinting) assays to check the identities and relationships of some samples, continuing work started by Rachel Merrigan in 2011. The final draft of the paper was circulated to all authors on 18th December for checking prior to submission in January 2013. During the writing of this paper, we had the promoter of the gene *KHDRBS3* sequenced in the members of three VUR families that showed linkage to the region surrounding it, and variants found were investigated in the lab and the results included in the paper.
2. Investigation of genetic variants in the major transcript, Isotype b, of the gene *ROBO2*. This is one of the many genes and other genomic regions sequenced in VUR index cases in 2009-2011 (Item 2 of the summary of work in 2007-2011). All 26 exons, with intronic margins, and 1 Kb of the promoter of Isotype b had been sequenced. During 2012 the 99 variants reported by sequence-analysis software were evaluated for veracity, evolutionary conservation and functional effect, and those of possible pathogenic consequence were investigated by genotyping family members of index cases having a selected variant, to look for segregation with VUR, and then genotyping BioBank control samples if the variant did segregate with VUR. All of the interns and students played some part in this work (except Michael Vogl). The results were written up for publication and submitted to Kidney International on 7th August. One reviewer made repeated numerous objections, requiring three rounds of extensive revision, and

the paper was submitted for the fourth time on 22nd November, and accepted on 20th December, with still a few more revisions required. During the preparation of this paper, we sent samples from 250 index cases for sequencing of the promoter and the two unique exons of Isoform a of *ROBO2*, but it was decided to leave the investigation of the variants in these regions for a subsequent paper.

3. Analysis of the results of whole genome-sequencing of nine members of an extended VUR family and an unrelated individual from a family in which clear cell renal cell carcinoma was segregating with a 2;3 chromosomal translocation through the same band in which we found our highest linkage to VUR in our original genome scan, 2q37.3 (Item 5 of the summary of work in 2007-2011). 713,883 variants were identified in the genomes of the extended family, and these were subjected to extensive bioinformatic analysis, and candidates for the mutation causing VUR were reduced to 14 single-nucleotide variants and a small number of multinucleotide inserting variants (analysis not yet completed). The translocation was found and bioinformatic investigation of the genes surrounding the breakpoints on both chromosome revealed that the closest gene to the breakpoint on Chromosome 2, *CXCR7* is overexpressed in >50% of renal cell carcinomata, so samples from the tumours of two family members were sent (from the lab of our collaborators in Melbourne) to the laboratory in Italy with published the CXCR7 results.
4. In odd moments, work was also begun on a discussion paper on the complexities of genetic analysis of VUR.
5. Michael Vogl analysed chromatograms of sequencing of genomic amplicons within our chromosome 13 linkage peak (another region included under Item 2 of the summary of work in 2007-2011). There is more work to be done on this region before we have enough information for publication.
6. DNA samples from our index cases were sent, at her request, to Helen Stuart in Manchester, to investigate for mutations in the gene *HPSE2*, which she had found to be one cause of the recessive disorder, Urofacial Syndrome. Only two heterozygous variants were found in any of our patients that would change amino-acids in the protein, and one of these did not segregate with VUR in the family concerned, so she decided that she did not have enough information to publish.

10.2 Group of Dr Sally Ann Lynch

The disorders

Our research group has a broad interest in genetic disorders causing malformation in children. We have a specific interest in disorders found in the Irish Traveller population and have built up some expertise in this area. The majority of disorders we study are rare and, in

each case, the gene responsible for the disease is unknown. The laboratory work on this project is being led by Dr Jillian Casey working in National Children's Research Centre.

Currently we are working on:

- Dilated cardiomyopathy and retinal dystrophy: a disorder causing cardiac anomalies and leading to progressive deterioration of vision
- Skeletal immunodysplasia: a disorder resulting in recurrent infections and skeletal anomalies
- Microcephaly and developmental delay in the Irish Traveller population: a neurodevelopmental disorder resulting in small head/brain size
- Primary ciliary dyskinesia in the Irish Traveller population: a respiratory disorder involving chronic recurrent infections in the lungs, ears and sinuses.
- Arthrogryposis in the Irish Traveller population: a disorder that limits movement in one or more joints of the body
- Infantile liver failure in the Irish Traveller population: a disorder involving recurrent liver dysfunction, anaemia, seizures and developmental delay

Progress during 2012:

- Dilated cardiomyopathy and retinopathy: Exome sequencing was undertaken and identified the cause of this rare disorder in the affected pair of siblings. Both children have novel genetic variants in *ALMS1*, a gene associated with Alstrom syndrome. As a result of this finding, we were able to provide a diagnosis for the family and patient management has been altered in line with their new diagnosis.
- Primary ciliary dyskinesia: Together with Dr Dubhfeasa Slattery (TSCH) we performed exome sequencing for three Irish Traveller families with primary ciliary dyskinesia of unknown genetic cause. The analysis revealed that the disorder is caused by a different disease gene in each family, which was unexpected. One family have a new mutation in a known PCD gene and our collaborator, Dr Breandan Kennedy (UCD), has created a zebrafish model for this disease gene. Novel candidate genes have been identified in the remaining two families and molecular studies are in progress together with Prof Oliver Blacque (UCD) and Prof Jeremy Simpsons (UCD) to determine how mutations in these genes affect ciliary function.
- Microcephaly: Homozygosity mapping and exome sequencing was undertaken in three Irish Traveller families with microcephaly and developmental delay. One family is from the UK and was assessed by our collaborator Dr Helen Murphy (Manchester). As microcephaly is a very heterogeneous disorder we are analysing the data of each family independently as it is not clear if they all share the same disease gene. Patients from two of the families share a large homozygous region on chromosome 11 which is currently being investigated for potential disease mutations.

- Infantile liver failure: In collaboration with Dr Ellen Crushell (NCIMD), we discovered mutations in leucyl trna synthetase (LARS) as a novel cause of infantile liver failure in the Irish Traveller population. We have used our research findings to develop a simple blood-based genetic test that has avoided the need for liver biopsies in recent patients. Additionally, we have instigated new studies with Dr Jacintha O' Sullivan (TCD) and Dr Niamh Lynam-Lennon (TCD) to investigate how genetic defects in LARS give rise to recurrent liver dysfunction. This is the first step towards developing possible therapeutic strategies.

Neurogenetics:

We also through our collaboration with Professor Mary King at the Children's University Hospital in Temple Street and with Dr Raymond Murphy in Tallaght (AMNCH) developed a number of neurogenetics projects. The laboratory work on these projects is being led by Dr Judith Conroy working in Dr Sean Ennis' laboratory at UCD. These disorders are extremely rare and identification of the genetic causes of these disorders is the first step in better understanding the molecular mechanisms that cause the disorders and developing treatments.

These projects include:

- Landau-Kleffner syndrome – an extremely rare form of rolandic epilepsy that is characterised by verbal auditory agnosia, clinical seizures, and epileptiform dischanrges during sleep. Genome-wide genotyping and methylation, array CGH and exome sequencing analysis was undertaken in 2 sets of discordant monozygotic twins and 11 isolated cases. No single common gene was identified.
- Episodic ataxia – Together with Dr Raymond Murphy (AMNCH) we collected DNA samples from many members of a large Irish family with autosomal dominant episodic ataxia where the genetic basis was unclear. Linkage analysis identified a novel linkage peak (1p36.13-p34.3) with a LOD score of 3.3. Exome sequencing was performed on a subset of family members and 2 candidate variants were identified, including one in UBR4 a gene known to interact with the internal calcium sensor calmodulin.
- Epileptic encephalopathy – Epileptic encephalopathies are severe brain disorders of early age that manifest with: (1) electrographic EEG paroxysmal activity that is often aggressive, (2) seizures that are usually multi-form and intractable, (3) cognitive, behavioural, and neurological deficits that may be relentless, and (4) sometimes early death. Professor Mary King is the principal investigator of the project which involves over 60 patient samples in whom the genetic cause remains to be identified. Dr Nicholas Allen is the lead researcher on this project and has been co-ordinating the clinical assessments on the patients. Dr Conroy has been doing the analysis. Samples have been collected, DNA extracted where necessary, and prepared for exome sequencing. The initial subset of samples has been sent for sequencing and the data analysis will be undertaken when data is received.

- Ptosis – A large family with ptosis, mild intellectual difficulties, obesity and minor additional dysmorphic features has previously been identified. Linkage analysis identified two novel loci. These were located on chromosomes 2p16.3-p15 (12.39Mb, rs6752658-rs1211158) and 10q26.2-26.3 (1.91Mb, rs9418809-rs995190). The DNA of a number of affected and unaffected family members was sent for exome sequencing. Following data analysis no candidate disease variant/gene was identified, indicating that this may be a genetic disorder in which the mutation lies outside the exonic region of the genome. Further studies are continuing.

The genetic problem

While individually rare, these diseases collectively create a tremendous burden of suffering: childhood malformations account for 21% of all infant deaths, and are responsible for more than 10% of paediatric hospital admissions. Most genes that cause rare disorders have not yet been found, mainly because gene-discovery studies are difficult to perform when there are only a few patients with the disorder. Recently a new technology, called Next-Generation Sequencing, has been developed which allows an individual's entire genetic code (~22,000 genes) to be analysed in a single experiment. This technology has revolutionised the study of rare genetic disorders because it is now possible to find disease-causing genes using a relatively small number of patients. Our own research confirms this; we successfully identified several new disease genes in Irish families, five of which were isolated by analysing the genetic sequence of an individual patient.

The projects

We propose to identify the genes and mutations responsible for the rare genetic disorder in each family using cutting-edge technologies such as Next-Generation Sequencing. Our aim is to identify disease genes so that these families can be offered accurate genetic counselling. We will also use our research findings to develop simple blood-based genetic tests that can be used for diagnostic and carrier testing and can avoid the need for invasive diagnostic tests (such as liver and muscle biopsies). The tests will allow for earlier diagnosis in future children (as yet unborn) and improved patient management. Disease gene identification means that we can offer immediate advice on recurrence and prevention to the family. It also provides a better understanding of disease and allows us to explore possible treatments. The long term goal is to develop a comprehensive panel of diagnostic tests for rare disorders "common" in Ireland.

Our projects are done in collaboration with local clinicians including Dr Ellen Crushell (Infantile liver failure) Dr Dubhfeasa Slaterry (Primary Ciliary Dyskinesia).

Summary of work during 2012

We had some success over 2012 and specifically at the Irish Society of Human Genetics Dr. Jillian Casey, NCRC Crumlin was awarded the best PostDoc oral presentation and Dr. Judith Conroy, UCD was awarded the best Postdoc Poster:

We have had some success in isolating genes in this population and have now built up a large cohort of data that can allow a faster analysis of the data as we have background information on many normal variants that are found in this population.

Grants awarded or currently active in 2012

Sally Ann Lynch
Principal investigator for the following grants:

Funding agency	Award amount	Date
Health Research Board KEDS scheme	€9,999	Dec 2012-Dec 2013
Children's Fund for Health, Temple Street University Hospital	€4,783.33.	June 2012-June 2013
Medical Research Charities groups [NCRC/HRB]	€95,580	Oct 2011-Oct 2013
Children's Fund for Health, Temple Street University Hospital.	€39,580.	Dec 2011-.Dec 2012

Grants submitted & awaiting outcome

HRB Population Health Awards October 2012

Publications

Parental insertional balanced translocations are an important cause of apparently de novo CNVs in patients with developmental anomalies. Nowakowska BA, de Leeuw N, Ruivenkamp CA, Sikkema-Raddatz B, Crolla JA, Thoelen R, Koopmans M, den Hollander N, van Haeringen A, van der Kevie-Kersemaekers AM, Pfundt R, Mieloo H, van Essen T, de Vries BB, **Green A, Reardon W**, et al Eur J Hum Genet. **2012** Feb;20(2):166-70. PMID: 21915152

A novel approach of homozygous haplotype sharing identifies candidate genes in autism spectrum disorder. Casey JP, Magalhaes T, Conroy JM, Regan R, Shah N, Anney R, Shields DC, Abrahams BS, Almeida J, Bacchelli E, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bolton PF, Bourgeron T, Brennan S, Cali P, Correia C, Corsello C, Coutanche M, Dawson G, de Jonge M, Delorme R, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Foley S, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Green J, Guter SJ, Hakonarson H, Holt R, Hughes G, Hus V, Igliozzi R, Kim C, Klauck SM, Kolevzon A, Lamb JA, Leboyer M, Le Couteur A, Leventhal BL, Lord C, Lund SC, Maestrini E, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Merikangas A, Miller J, Minopoli F, Mirza GK, Munson J, Nelson SF, Nygren G, Oliveira G, Pagnamenta AT, Papanikolaou K, Parr JR, Parrini B, Pickles A, Pinto D, Piven J, Posey DJ, Poustka A, Poustka F, Ragoussis J, Roge B, Rutter ML, Sequeira AF, Soorya L, Sousa I, Sykes N, Stoppioni V, Tancredi R, Tauber M, Thompson AP, Thomson S, Tsiantis J, Van Engeland H, Vincent JB, Volkmar F, Vorstman JA, Wallace S, Wang K, Wassink TH, White K, Wing K, Wittemeyer K, Yaspan BL, Zwaigenbaum L, Betancur C, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Geschwind DH, Haines JL, Hallmayer J, Monaco AP, Nurnberger JI Jr, Pericak-Vance MA, Schellenberg GD, Scherer SW, Sutcliffe JS, Szatmari P, Vieland VJ, Wijsman EM, **Green A**, Gill M, Gallagher L, Vicente A, **Ennis S**.
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Perrault syndrome: further evidence for genetic heterogeneity. Jenkinson EM, Clayton-Smith J, Mehta S, Bennett C, **Reardon W**, **Green A**, Pearce SH, De Michele G, Conway GS, Cilliers D, Moreton N, Davis JR, Trump D, Newman WG.
J Neurol. 2012 May;259(5):974-6.

Common variation near CDKN1A, POLD3 and SHROOM2 influences colorectal cancer risk. Dunlop MG, Dobbins SE, Farrington SM, Jones AM, Palles C, Whiffin N, Tenesa A, Spain S, Broderick P, Ooi LY, Domingo E, Smillie C, Henrion M, Frampton M, Martin L, Grimes G, Gorman M, Semple C, Ma YP, Barclay E, Prendergast J, Cazier JB, Olver B, Penegar S, Lubbe S, Chander I, Carvajal-Carmona LG, Ballereau S, Lloyd A, Vijayakrishnan J, Zgaga L, Rudan I, Theodoratou E; The Colorectal Tumour Gene Identification (CORGI) Consortium, Thomas H, Maher E, Evans G, Walker L, Halliday D, Lucassen A, Paterson J, Hodgson S, Homfray T, Side L, Izatt L, Donaldson A, Tomkins S, Morrison P, Brewer C, Henderson A, Davidson R, Murday V, Cook J, Haites N, Bishop T, Sheridan E, **Green A**, et al. Nat Genet. **2012** May 27;44(7):770-776. doi: 10.1038/ng.2293. PMID: 22634755

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Glessner JT, **Green A,** Green J, Guter SJ, Heron EA, Holt R, Howe JL, Hughes G, Hus V, Igliozzi R, Jacob S, Kenny GP, Kim C, Kolevzon A, Kustanovich V, Lajonchere CM, Lamb JA, Law-Smith M, Leboyer M, Le Couteur A, Leventhal BL, Liu XQ, Lombard F, Lord C, Lotspeich L, Lund SC, Magalhaes TR, Mantoulan C, McDougle CJ, Melhem NM, Merikangas A, Minshew NJ, Mirza GK, Munson J, Noakes C, Papanikolaou K, Pagnamenta AT, Parrini B, Paton T, Pickles A, Posey DJ, Poustka F, Ragoussis J, Regan R, Renshaw K, Roberts W, Roeder K, Roge B, Rutter ML, Schlitt S, Shah N, Sheffield VC, Soorya L, Sousa I, Stoppioni V, Sykes N, Tancredi R, Thompson AP, Thomson S, Tryfon A, Tsiantis J, Van Engeland H, Vincent JB, Volkmar F, Vorstman J, Wallace S, Wing K, Wittemeyer K, Wood S, Zurawiecki D, Zwaigenbaum L, Bailey AJ, Battaglia A, Cantor RM, Coon H, Cuccaro ML, Dawson G, **Ennis S**, et al.. Hum Mol Genet. **2012** Jul 26.

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Allogeneic hematopoietic stem cell transplantation for BCR-FGFR1 myeloproliferative neoplasmpresenting as acute lymphoblastic leukaemia. Karl Haslam, Stephen E. Langabeer, **Johanna**

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Incidence of the BRAF V600E mutation in chronic lymphocytic leukaemia and prolymphocytic leukaemia. Stephen E. Langabeer, Fiona Quinn, David O'Brien, Anthony M. McElligott, **Johanna Kelly**, Paul V. Browne, Elisabeth Vandenberghe. Leukaemia Research, Volume 36, Issue 4, April 2012, Pg 483-484

A novel, variant BCR-ABL1 transcript not detected by standard real-time quantitative PCR in a patient with chronic myeloid leukaemia. S. L. McCarron, K. Haslam, **J. Kelly,** C. Duggan, S. E. Langabeer. International journal of laboratory hematology. 2012. Volume 34, e1-e2.

Characterization of the chromosomal translocation t(10;17)(q22;p13) in clear cell sarcoma of kidney. O'Meara E, Stack D, Lee CH, Garvin AJ, **Morris T**, Argani P, Han JS, Karlsson J, Gisselson D, Leuschner I, Gessler M, Graf N, Fletcher JA, O'Sullivan MJ. J Pathol. 2012 May;227(1):72-80.

11 PLATFORM PRESENTATIONS

Kelly J, Barton L, Morris T, Smith O, Betts DR Concurrent translocations involving MLL (11q23) and MYC (8q24) in an infant B-cell acute lymphoblastic leukaemia (ALL). Irish Society of Human Genetics, Dublin, Ireland. September 2012

Nicola Harper, Andrew Green The complexity of counselling families for double heterozygosity in Inherited Cardiac Conditions. Irish Society of Human Genetics, Dublin, Ireland. September 2012

Melissa Rogers, Karen Meaney, Trudi McDevitt, Philip Mayne, Geraldine Roche, David E. Barton. NBS Screening for CF in Ireland – First Anniversary Review. Irish Society of Human Genetics, Dublin, Ireland. September 2012

Mark McCormack, Gerard D. O'Connor, Erin L. Heinze[3], Kevin V. Shianna, Judith Conro[4], Sean Ennis, David B. Goldstein, Norman Delanty, Gianpiero L. Cavalleri. Whole exome sequencing in Irish pedigrees identifies novel mutations for epilepsy predisposition. Irish Society of Human Genetics, Dublin, Ireland. September 2012

Rea G, Stallings RL, Mullarkey M, McKinstry CS, McManus D, Morrison PJ*.
Sub-Cortical White Matter Abnormalities due to previously undescribed*de novo* 14q12-13 duplication. Irish Society of Human Genetics, Dublin, Ireland. September 2012

J. Conroy, P. McGettigan, K. Collins, B Parry-Fielder, M. Moran, O O'Mahoney, D. Webb, S. Ennis, M. King, S.A. Lynch. Platform Presentation. Exome sequencing – an approach to unlock the secrets of rare disorders. Children's University Hospital Audit and Research Day, Temple Street, Dublin, Ireland. December 2012.

The hope and hype of exomic sequencing J Conroy, P McGettigan , O Walsh (3), B McCoy (3), C Albertyn, A McGillivary, M Moran , N Goggin, M Ahmed, O O'Mahoney, C Korff , T Deonna, D Hanrahan , M Earley , D Webb, S Murphy, R Murphy, S Ennis, M King, SA Lynch & Sean Ennis North Dublin Hospital Group Conference. Rotunda hospital November.

John M. Darlow, Mark G. Dobson, David E. Barton & Prem Puri, The genetics of vesicoureteric reflux. *National Children's Research Centre Symposium*, Dublin, December 2012.

P. McGettigan, J. Casey, J. Conroy, S. Ennis. Platform Presentation. Identifying causes of rare Mendelian disease in humans using while exome sequencing. VIBE, Dublin. November 2012.

J. Casey, P. McGettigan, N. Alkazemi, P. Maguire, B. Kennedy, D. Brosnahan, E. Treacy, K. Walsh, S. Ennis, S.A. Lynch. Exome analysis and cardiomyopathy: The Lazarus story. Irish Society of Human Genetics, Dublin, Ireland. September 2012. (won best post-Doc award)

S.A. Lynch, J. Turner, S. Ennis, J. Casey. Making matches- linking large Irish Traveller pedigrees to; a) aid with disease gene identification & b) understand the demographics of this endogamous community. Irish American paediatric meeting Belfast Sept 2012.

S A Lynch, P Mcgettigan, S Ennis, J Casey. Recessive mutations in MCM4/PRKDC cause a novel syndrome characterised by a primary immunodeficiency & impairments in DNA repair. Joint Belfast/Dublin clinical genetics meeting, Daisy Hill Hospital, Newry, June

Prof Andrew Green Consent – wider discussion & comparison of consent in different countries. Joint Belfast/Dublin clinical genetics meeting, Daisy Hill Hospital, Newry June

J. Conroy, P. McGettigan, M. Moran, O. O'Mahoney, D. Webb, M. King, S. Ennis, S.A. Lynch. Landau-Kleffner syndrome: CNV and exome sequencing analysis. Neuroscience Ireland, Dublin, Ireland. September 2012.

J. Casey, M. Nobbs, P. McGettigan, S.A. Lynch, S. Ennis. A single mutation that affects two genes; MCM4 and PRKDC cause a primary immunodeficiency, disorder of DNA repair and familial glucocorticoid deficiency. Our Lady's Children's Hospital Research & Audit Day, Dublin,. May 2012.

J. Casey, D. Slattery, J. Conroy, R. Regan, S. Ennis, S.A. Lynch. Exome sequencing and the challenge of rare disorders. National Children's Research Centre Seminar Series, Our Lady's Children's Hospital, Crumlin, Dublin, January 2012.

J. Casey, P. McGettigan, B. Kennedy, S. Ennis, A. McCann, SA. Lynch. Identification of recessive disease genes for primary ciliary dyskinesia, microcephaly and dilated cardiomyopathy. *National Children's Research Centre Symposium*, Dublin, December 2012.

Jillian Casey, Invited speaker at Retina 2012 patient engagement day. Presentation entitled 'Your genome and the Next Generation'. Certus head office, Dublin, Ireland, November 2012.

Jillian Casey, Invited speaker at Dublin City of Science / ESOF 2012 public event 'Your Genes, Your Health, Your Future'. Presentation entitled 'What's in a Genome?' Royal College of Surgeons, Dublin, Ireland, September 2012.

12 Abstract from Meetings

1. 35th European CF Conference, Irish Society for Human Genetics
2. Professor Green was a chairperson at the European Breast Cancer in Young Women meeting in UCD on 8th-9th November, organised by the European School of Oncology

13 Poster Presentations

NBS for CF in Ireland, 1st Anniversary Review – Genetics, 35th European CF Conference, Dublin 06/06/2012

NBS for CF in Ireland, 1st Anniversary Review – Genetics Irish Society for Human Genetics, RCSI, Dublin 03/09/12

NBS for CF in Ireland, 1st Anniversary Review - Genetics Medical Grand Rounds - TSH, Dublin 17/08/2012

J. Casey, A. Green, P. McGettigan, J. Conroy, R. Regan, S. Ennis, S.A. Lynch. . Next-generation diagnostics for rare disorders in the Irish population. New Frontiers Symposium: Personal Genomics, Nijmegen, Netherlands. December 2012.

J. Conroy, P. McGettigan, D. Webb, O. Walsh, C. McDonagh, S.M. Murphy, R. Murphy, S. Ennis, S.A. Lynch. Combining linkage mapping with exome sequencing data. Ataxia Research Conference, London, UK. November 2012.

S.A. Lynch, J. Turner, S. Ennis, J. Casey. Making matches- linking large Irish Traveller pedigrees to; a) aid with disease gene identification & b) understand the demographics of this endogamous community. UK Dysmorphology Meeting. Manchester, UK. October 2012.

S.A. Lynch, J. Turner, J. Casey. Making matches: linking large Irish Traveller pedigrees as a way of helping gene identification. Irish Society of Human Genetics, Dublin, Ireland. September 2012.

J. Conroy, P. McGettigan, K. Collins, B. Parry-Fielder, M. Moran, O O'Mahoney, D. Webb, M. King, S. Ennis, S.A. Lynch. Identifying the genetic basis of Landau-Kleffner Syndrome. Irish Society of Human Genetics, Dublin, Ireland. September 2012. (won best Post-Doc poster)

J. Conroy, P. McGettigan, O. Walsh, C. McDonagh, M. Moran, O. O'Mahoney, D. Webb, S.M. Murphy, R. Murphy, M. King, S. Ennis, S.A. Lynch.. Exome sequencing in rare neurological conditions: The advantages of linkage mapping. Neuroscience Ireland, Dublin, September 2012.

L. Bradley, T. Dabir, C. Murphy, D. Murray, A. McGillivary, S.A. Lynch. A retrospective analysis of the prevalence of craniosynostosis on the island of Ireland. Irish Society of Human Genetics, Dublin, September 2012.

J. Casey, A. Green, P. McGettigan, J. Conroy, R. Regan, S. Ennis, S.A Lynch.. An alternative approach to research: Technology driven research for rare disorders in the Irish population. UK Clinical Research Facility Network Conference, Dublin, July 2012.

J.P. Casey, M. Nobbs, P. McGettigan, S. Lynch, S. Ennis. Recessive mutations in MCM4/PRKDC cause a novel syndrome characterised by a primary immunodeficiency and impairments in DNA repair. European Society of Human Genetics, Nurnberg, Germany. June 2012.

S. A. Lynch, M. Akram, N. Goggin, M. Earley, S. Ennis, J. Conroy. Ptosis, arched eyebrows, hypernasal speech, obesity & mild learning disability- a clinical & mapping study. European Society of Human Genetics, Nurnberg, Germany. June 2012.

J. Conroy, P. McGettigan, O Walsh, C. McDonagh, R. Murphy, D. Webb, S. Ennis, S.A. Lynch. A novel locus for autosomal dominant episodic ataxia. Our Lady's Children's Hospital Research and Audit Day, Dublin, May 2012.

J. Kelly, O. P Smith, A. O'Marcaigh, D. R Betts. Incidence of Cytogenetic Aberrations in Paediatric Acute Lymphoblastic Leukaemia presenting in the period 2006-2010. OLCHC Clinical Audit Day 2012.