Dying to see you? Deaths on a clinical genetics waiting list in the Republic of Ireland; what are the consequences?

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Abstract

Attempts to put a value on a clinical genetic consultation are challenging as outcome measures are not easily quantified. One technique is to consider the negative consequences to a referred patient who is never seen. In order to estimate possible negative effects and by default the value of a genetics consultation; we sought to identify the consequences both to the proband, who died awaiting appointment, and their relatives. We audited 45 referrals to our service who died on our waiting list since 2008. Of these, 39/45 were new referrals, and the remainder, 6/45, died awaiting a follow up appointment. Relatives from 14/45 (31%) families have been counselled since the proband's death. We estimated a minimal total of 207 living first degree relatives to 45 probands. The majority (30/45) were referred for cancer risk estimation (1 predictive, 29 diagnostic), 11 developmental delay/dysmorphology referrals, 3 cardiac genetic referrals, (2 predictive testing, 1 segregation analysis) and 1 a referral for early onset dementia. The deaths of 17/45 cases were judged by us as having potentially significantly impacted the health of 76 first-degree relatives; 13/45 have potentially moderately impacted the health of 57 first-degree relatives; 12/45 posed a minimal impact to their relatives; and in 3/45 cases families were fully counselled. For each proband, significantly or moderately negatively impacted ($n = 30$), they have a minimum of 4.4 first-degree relatives, range 1–11, total = 133.

Keywords Time to wait · Deaths on a waiting list · Clinical genetics · First degree relatives

Introduction

As a non-acute specialty, traditional models of clinical genetic practice do not routinely involve patient management. As such, deaths on a clinical genetics waiting list do not generate alarm amongst health service providers. In contrast, patient deaths on acute medical or surgical specialties would generate investigation and action. However, the tragedy of these deaths is that the negative consequences impact not just the proband but also their healthy relatives as a possible hereditary disorder may remain undiagnosed and/or under-investigated, and opportunities for further investigation, surveillance and/or prophylactic surgery unexplored. Advancements in genomic technology resulted in increasing demand for genetic services

worldwide. This coincided with a global recession leading to austerity measures impacting health services in the Republic of Ireland (ROI). A perfect storm resulted which led to a deteriorating clinical genetics waiting list. Staffing levels of clinical genetic specialists (consultants, trainees or genetic counsellors) are much lower in the ROI than other European or western countries (Lynch and Borg 2016). There is only one clinical genetic service in the ROI, based in Dublin, which accepts all types of referrals, both general and cancer, including foetal medicine, paediatrics and adult cases. Patients are referred from all over the Irish Republic. Up to 40% of the ROI population (total 4.9 million) live within the greater Dublin area, and 37% live in rural areas with the remainder living in urban areas outside of Dublin. The percentage of referrals to our service living outside of Dublin reflects the population trends. The clinical genetic service is based in a paediatric hospital with no ring fenced budget. There is a separate adult cancer genetic service run by an oncologist also based in Dublin. The health service allocates public monies to the hospital for distribution throughout all the specialties within the hospital. Other factors contributing to the pressures on the genetics service include the fact that the ROI has (a) the

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highest birth rate in the EU; (b) no access to termination of pregnancy until recently (January 2019), resulting in a high live-born malformation rate; and (c) large pedigrees, average family size has remained greater than equivalent western countries for decades (Fahey 2001). Each Irish extended 3 generation family tree has on average 64 relatives in comparison to 19 for an equivalent English/Scottish/Welsh pedigree (McVeigh et al. 2019). This generates a greater cascade screening workload. The current average waiting time for a routine appointment is up to 3 years and ~ 18 months for a priority appointment, and these prolonged waiting times are longstanding (approximately 5 years). A consequence of waiting times of this length is that patients have died prior to appointment $n = 45$; 18 of which we were aware of from 2008 to 2017 (10 year period); and 27 cases were recorded since 2018.

Whilst the death of the proband is recorded, the consequence to their relatives is not captured. We were prompted to do this study following a risk assessment of our waiting list, as we grew increasingly alarmed about possible negative impact to the health of relatives. We reviewed the records of patients who died on our waiting list to identify possible adverse consequences and quantify the number of relatives adversely affected.

We recognize well-resourced clinical genetic centres do not encounter the volume of deaths on waiting lists as their waiting times are a fraction of ours. However, it is important to note that the findings from our study are applicable to those families where a proband fails to attend their appointment or where a clinician neglects to refer a patient with a hereditary disorder.

Methodology

A retrospective chart and clinical genetic database review were performed. Data was collected by proforma and transferred onto a spreadsheet for analysis. Dates of deaths were obtained from <https://deathevents.gov.ie/> if not already recorded on hospital systems. We noted date we were first aware of the death and who informed us of death. We reviewed the triage process to re-evaluate if the decision-making regarding prioritization was correct for the clinical details in the referral letter. In addition, where available, genetic databases, obituary notices and genetic charts were reviewed to identify the number and gender of living first-degree relatives (FDR). This study was done as part of clinical audit and usual practice www.hrb.ie/.

We grouped the consequences to the families under 4 headings (significant, moderate, minimal and no negative impact) and defined them as follows:

- 1) A significant negative impact is one where there might be a risk of recurrence in a relative, who has no opportunity to avail of surveillance and might not be aware of their

risk and in whom we could have ameliorated their risk if we had seen their relative. For these families, in addition to the proband not being seen, there was no contact with other family members, no genetic testing was performed and no DNA was stored.

- 2) A moderate negative impact is one where DNA on the proband was stored or a predictive test is available but we have had no contact with any family member to activate the sample and we are unsure if the genetic risk information has been communicated to the at risk relatives and are unsure if they are being offered surveillance. In others, whilst the referral was for predictive testing, no DNA on the proband was stored and no offspring came forward raising concerns that they might not be aware of their risk.
- 3) A minimal negative impact was defined in a number of ways as the referrals were a very diverse group: (a) families who were seen and DNA was stored/tested but in whom the adult proband did not get the opportunity to meet with a member of the clinical genetics team to discuss their condition and how we would best advise their at risk relatives, and (b) for some paediatric cases, we have included those families where the parents were seen and counselled but it will remain difficult to interpret variants of unknown significance without being able to examine the proband.
- 4) Where a family was fully counselled with no adverse consequence, this was judged as having no negative impact in this study.

Limitations

As most patients had never been seen, there were missing pedigree data on 25/45 referrals, in 10/25 we had no pedigree information whatsoever, in the remaining 15 we had sourced information from family history questionnaires in 8 and from obituary notices in 7 referrals, see Fig. 1. We noted missing pedigree data from some of the family history questionnaires; patients sometimes detailed affected relatives only and failed to document unaffected at risk FDR.

We were not able to ascertain other genetic risks within a pedigree that might have come up in consultation that have impacted on the family. For example, we know a second genetic diagnosis was present in 3/20 where a pedigree had been taken, it is therefore likely we have underestimated negative consequences.

Results

During the time period (2008–2019) we received 48,622 referrals with an average of 4051 per year, range 3425–4889.

Fig. 1 Estimation of the number of living first-degree relatives (FDR) by sources of information. Total number = 207 living FDR, FHQ = family history questionnaire

The numbers of referrals to our service is low at 0.84/1000 population in comparison to 5 UK units; (McVeigh et al. 2019, mean & median referral numbers across 6 centres [5 UK and ROI] = 2.05/1000 population; range 0.84/1000–3/1000).

In February 2009, we changed our practice and introduced a system where face to face appointments were replaced with information letters/ leaflets for some common disorders (Trisomy 21, Neural tube defects, Non syndromic cleft lip/palate, benign hypermobility), in an attempt to manage the waiting list. This resulted in a reduction in referrals; in addition, the birth rate in Ireland dropped 20% over the study interval (our referral rate dropped by 13.5% over the same time period), likely due to a combination of these factors (see Fig. 2). With regard to the 45 probands who died; the age at referral ranged from 10 days to 85.01 years; (mean 45.93 years, median 53.94 years). The age range at death was from 47 days to 85.86 years; (mean 46.15 years, median 55.6 years); 17/45 were males; and 28/45 were female, reflecting the proportion that were referred with a history of breast cancer. In 4 cases the deaths were due to causes unrelated to the family disorder. Relatives from 14/45 (31%) families have been counselled since the proband's death.

With regard to the 6 probands who were on the follow-up waiting list, 5/6 died awaiting results, the 6th died having been re-referred with the same cancer diagnosis, having previously declined testing (see Fig. 1). Of the 30 cancer referrals, 1 referral was for predictive testing (see Fig. 4). Several of the cancer deaths occurred in probands referred after their second ($n = 9$) or third ($n = 3$) cancer diagnosis, indicating delayed referral from the outset, 5/12 having had their first cancer diagnosis 20 or more years prior to referral. The 3 cardiac referrals comprised a cardiomyopathy referral, a referral with a family history of Marfan syndrome and 1 long QT syndrome (see Fig. 3).

In total, 30/45 probands had no DNA stored and 14 had DNA stored (see Fig. 3). One dysmorphology case was diagnosed on karyotyping (not requiring DNA testing). Only 9/39 (23%) probands, who had never been seen by Clinical Genetics, had DNA stored.

In 11/45 (all developmental delay/dysmorphic syndrome), the risk was largely confined to the parents although for those males without a diagnosis (3/11), there remains a possibility of an X-linked disorder with reproductive risks to maternal relatives. In the rest, $n = 34$, all potentially autosomal dominant disorders with reduced penetrance, there are risks to all FDR

Fig. 2 Fluctuation in referral numbers per year and livebirths over study period. The year of introduction of various initiatives to mitigate the negative factors impacting the waiting list (w/l) are indicated by the numbered arrows: (1) Leaflets introduced in lieu of appointments for common disorders (Clefting, neural tube defects, Hypermobility, Trisomy 21). (2) Mainstreaming by oncologists for ovarian cancer testing. (3) Letter to oncologists requesting communication regarding probands that were terminally ill and that necessitated urgent review

Fig. 4 Adult referrals, consequences with regard to numbers of FDR requiring surveillance. FDR first-degree relatives, f female, m male, Br breast, ov ovarian, ca cancer. (1) <https://www.hiqa.ie/sites/default/files/2017-01/HTA-breast-cancer-technical.pdf> date accessed 19/08/2020. (2) <https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/diagnosis-and-staging-of-patients-with-ovarian-cancer.pdf> (date accessed 19/08/2020). (3) Grazioli G, Sanz de la Garza M, Vidal B,

et al. Eur J Prev Cardiol. (2017) Prevention of sudden death in adolescent athletes: Incremental diagnostic value and cost-effectiveness of diagnostic tests. Sep;24(13):1446–1454. doi: <https://doi.org/10.1177/2047487317713328>. (4) https://www.hiqa.ie/sites/default/files/2017-01/HTA_population_based_colorectal_cancer_screening_programme.pdf (date accessed 19/08/2020)

(see Fig. 3). In 4/34 the family mutation was known (3 cancer, 1 cardiac), 0/4 had DNA stored but predictive genetic testing is available to at risk relatives if they are cognisant of this and choose to request it. DNA was stored on the proband only in 5/30 where no predictive test is available, meaning that risk stratification by genotype is not possible in those families unless another relative is diagnosed and tests positive (see Fig. 3).

The sources of information we used to estimate numbers of living FDR is outlined in Fig. 1. In addition to the living relatives, we identified a minimum of 14 first-degree deceased sibling relatives who had died of a similar cause to the referral reason.

The average time 39 probands were alive from triage until death (window of opportunity to see patients) was 308 days (6 follow-up cases were not included). We noted 12/39 probands died within 6 months of being referred (range 12–124), and for 27/39 referrals, the range was 141–898 days from triage to death. Unfortunately, 24/45 appointments were sent out posthumously. In 24/45 cases it was a relative who informed us of the death. With hindsight, 7/45 possibly could have been triaged onto a priority or urgent waiting list. The perceived impact to proband and relatives is outlined in Figs. 3 and 4.

Fig. 3 Impact of proband death: to proband and FDR with reference to referral type and DNA storage

Discussion

Clinical genetic appointments offer a unique opportunity to explain to probands the genetic basis of their (or their relatives) disorder and how it might impact on them and their family (Godard et al. 2003). Studies have shown that many affected with cancer are keen to attend clinical genetics with altruistic concerns for family members rather than their own health (Fraser et al. 2003). If a patient dies prior to a clinical genetics appointment there is a failure in some, to establish a genetic diagnosis, while in those who come with a genetic diagnosis, there is a failure to have clarified the risks and choices to them and their relatives including predictive testing, surveillance, prophylactic surgery and pre-natal options.

It is important to note that the consequences to relatives are mirrored in families where the proband fails to attend their clinical genetics appointment or who never get referred by their physician in the first place (Delikurt et al. 2015). Therefore, the results of our study are relevant beyond those that died as clinic nonattendance amounts to 7% of our appointments, a figure that is mirrored internationally (Humphreys et al. 2000).

Access to clinical genetic services in the ROI has been challenging since inception. There were only 4 consultant clinical geneticists providing a public service to a population of > 4 million during the study time period. Despite active management of the waiting list, prolonged waiting times continued and have contributed, in part, to the deaths on the waiting list. Some of the proband deaths we describe occur within all health systems. However, 28/45 (62%) died having waited > 6 months emphasizing inequity of care within Europe. Many patients would have been seen prior to death in neighbouring jurisdictions, as the window of opportunity to see them prior to their death exceeded the 47-day target in Germany (Schmidtke et al. 2020) or the 126-day UK NHS OPD waiting time target (<https://www.nhs.uk/using-the-nhs/nhs-services/hospitals/guide-to-nhs-waiting-times-in-england/>) (date accessed August 14, 2020).

In many cases, we wrote to the spouse following the death of the proband as they were the next of kin, but as the spouse is not a biological relative (unless the couple are consanguineous), they are not at risk of the disorder. None of the probands, to our knowledge, came from consanguineous unions. We found that only 31% of relatives sought advice after the proband's death. In addition, contact directly after a death is not an appropriate time for many families. As we do not have the contact details for the biological relatives nor have we the authority to contact them directly, the majority of families are not followed up by our service. We are uncertain if the relatives are aware of their risk and if they are partaking in surveillance programmes or preventative measures to reduce their risk.

Clearly, we had limited information from the genetic records as the patients were not seen and full pedigrees were only available in 44%. However, we would estimate that at least 133/207 of the FDR and a larger number of second-degree relatives are at risk. They may not be aware of their risk or availability of preventative measures to ameliorate their risk. It is important to stress that we have under-ascertained our numbers of FDR because of the limitation in our pedigree data. For example, we estimated an average of 26 FDR from the 10 probands (average 2.6 per proband) where information was sourced only from the referral letter. In contrast, we had a total of 90 FDR from 20 probands where we had taken pedigrees (average 4.7 per proband).

Unfortunately, the Irish health care system has not yet introduced unique patient identifiers (legislation is awaited through parliament). Electronic systems are individual to each hospital. Transfer of data from one hospital to another is hindered by data protection laws. These factors resulted in appointments being sent to deceased patients (some > 500 days after death).

The nature of this study meant we chose not to capture adverse consequences other than death. This resulted in skewing towards cancer genetic families. However, we have observed other significant adverse consequences of our waiting list such as (1) > 25 at risk pregnancies announced in clinic, 10 of whom had rushed pre-natal testing; (2) 4 recurrences of the family genetic disorder; and (3) 2 individuals whose relative developed a cancer which might have been prevented if the proband had been seen promptly.

We recognize a reluctance to refer to our service as referrers are aware patients face a prolonged wait and we surmise that contributed to our low referral rate in comparison to equivalent UK centres (McVeigh et al. 2019). In addition, we noted a delay in the referral of a number of probands who were much further on in their disease process indicating lack of understanding of the role of clinical genetics in some cancers (Delikurt et al. 2015). We therefore anticipate many other families in ROI who are at risk but are not aware of it due to lack of referral to our service or due to knowledge deficits on the part of the referrer as to the potential genetic component of their patient's disorder (Delikurt et al. 2015).

We appreciate that further mainstreaming of genetic testing would have ameliorated some of the negative consequences as DNA would have been stored and tested in those that met testing criteria. However, we noted in the 3 cases where DNA was stored, none of the families came forward to activate the sample at a later date. Collecting samples therefore requires decision-making and consent at source to ensure a clear pathway of action on a sample if the proband dies prior to testing. Recent reports regarding mainstreaming suggest (1) that the limitations of new technology are best explained by clinical genetic teams with patients responding better to ambiguous results having attended genetic services and (2) that

there is a shortfall in uptake of cascade testing in cancer families seeing an oncologist in comparison to those families that meet with a geneticist (Elliott and Friedman 2018; Flaum et al. 2020). Cascade testing is dependent on communication of genetic disorders via the proband, and often communication of risk is better to offspring than to siblings or more distant relatives (Cody et al. 2008). Genetic services have experience in methods that facilitate inter-family communication as this is an integral part of their service. It is naïve to expect other specialists to become proficient at this overnight when it is not routine practice.

It was not possible in this study to accurately estimate cost implications to the health service and society because of the absence of key data. Clearly, it is possible that a cancer might occur in an FDR that could have been prevented and the cost of treatment will exceed the cost of genetic testing. Quantifying excess costs of FDR surveillance is compounded by the fact that we do not know the age of the FDR or whether or not some of the FDR are being screened or taking preventative measures to reduce their risk. We have outlined costs of surveillance per individual and the number of FDR in Fig. 4, (<https://www.hiqa.ie/sites/default/files/2017-01/HTA-breast-cancer-technical.pdf>, <https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/diagnosis-and-staging-of-patients-with-ovarian-cancer.pdf>, Grazioli et al 2017, https://www.hiqa.ie/sites/default/files/2017-01/HTA_population_based_colorectal_cancer_screening_programme.pdf).

Conclusion

Our study highlights the potential for a multiplicity of negative impacts if a proband is not assessed including:

- 1 No genetic diagnosis precludes accurate risk assessment and preventative measures.
- 2 No DNA stored on affected individuals. The genetic basis of a secure clinical diagnosis is not established precluding risk stratification for at risk relatives.
- 3 Missed opportunities to engage with relatives if the proband is not counselled.
- 4 Missed opportunities to access surveillance or conversely relatives undergoing unnecessary surveillance as no predictive test for family.
- 5 Squandering of resources as relatives who are not gene carriers continue to have screening as genetic testing is not available to offer reassurance.
- 6 DNA is stored but without an examination it might prove difficult to assess a variant of unknown significance identified should NGS be performed post-mortem.
- 7 Segregation analysis is impeded precluding opportunities to classify a variant's pathogenicity

Since this submission, we have been informed of 3 further adult deaths, 2 cardiac and one cancer bringing the total to 48.

Author's contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sally Ann Lynch and Lisa Bradley. The first draft of the manuscript was written by Sally Ann Lynch, and Lisa Bradley commented on and revised all versions of the manuscript. All authors read and approved the final manuscript.

Data availability An anonymised spreadsheet with the data is available on request.

Compliance with ethical standards

Conflict of interest Dr. Sally Ann Lynch declares no conflict of interest. Dr. Lisa Bradley declares no conflict of interest.

Code availability Not applicable.

Ethics approval This study was done as part of clinical audit and usual practice in accordance with Irish Health and research regulation guidelines www.hrb.ie/

Consent to participate Not applicable.

Consent for publication Not applicable.

References

- Cody N, McDevitt T, Green AJ, Lynch SA (2008) Cascade screening in BRCA1/2 mutation carriers. *Ir Med J* 101(5):140–142
- Delikurt T, Williamson GR, Anastasiadou V, Skirton H (2015) A systematic review of factors that act as barriers to patient referral to genetic services. *Eur J Hum Genet* 23:739–745
- Elliott AM, Friedman JM (2018) The importance of genetic counselling in genome-wide sequencing. *Nat Rev Genet* 19(12):735–736. <https://doi.org/10.1038/s41576-018-0057-3>
- Fahey T (2001) Trends in Irish fertility rates in comparative perspective. *Econ Social Rev* 32:153–180
- Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, Mitchell CL, Badea D, Moon S, Hogg M, Hadjiyiannakis D, Clancy T, Schlecht H, Woodward ER, Crosbie EJ, Edmondson RJ, Wallace AJ, Jayson GC, Lalloo FI, Harkness EF, Evans DGR et al (2020) Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the north west of England. *Eur J Hum Genet*. <https://doi.org/10.1038/s41431-020-0692-y>
- Fraser L, Bramald S, Chapman C, Chu C, Cornelius V, Douglas F, Lucassen A, Nehammer A, Sutton S, Trivella M, Hodgson S (2003) What motivates interest in attending a familial cancer genetics clinic? *Fam Cancer* 2:159–168. <https://doi.org/10.1023/B:FAME.0000004621.38109.16>
- Godard B, Kääriäinen H, Kristoffersson U, Tranebjærg L, Coviello D, Aymé S (2003) Provision of genetic services in Europe: current practices and issues. *Eur J Hum Genet* 11(2):S2–S4 1018–4813/03
- Grazioli G, Sanz de la Garza M, Vidal B, Montserrat S, Sarquella-Brugada G, Pi R, Til L, Josep Gutierrez J, Josep Brugada J, Marta Sitges M (2017) Prevention of sudden death in adolescent athletes: incremental diagnostic value and cost-effectiveness of diagnostic tests. *Eur J Prev Cardiol* 24(13):1446–1454. <https://doi.org/10.1177/2047487317713328>

- https://www.hiqa.ie/sites/default/files/2017-01/HTA_population_based_colorectal_cancer_screening_programme.pdf. Accessed 19 Aug 2020
- <https://www.hiqa.ie/sites/default/files/2017-01/HTA-breast-cancer-technical.pdf>. Accessed 19 Aug 2020
- <https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/diagnosis-and-staging-of-patients-with-ovarian-cancer.pdf>. Accessed 19 Aug 2020
- <https://www.nhs.uk/using-the-nhs/nhs-services/hospitals/guide-to-nhs-waiting-times-in-england/> (date accessed 19/08/2020)
- Humphreys L, Hunter AG, Zimak A, O'Brien A, Komeluk Y, Cappelli M (2000) Why patients do not attend for their appointments at a genetics clinic? *J Med Genet* 37(10):810–815. <https://doi.org/10.1136/jmg.37.10.810>
- Lynch SA, Borg I (2016) Wide disparity of clinical genetics services and EU rare disease research funding across Europe. *J Community Genet* 7(2):119–126. <https://doi.org/10.1007/s12687-015-0256-y>
- McVeigh TP, Donnelly D, Al Shehhi M, Jones EA, Murray A, Wedderburn S et al (2019) Towards establishing consistency in triage in a tertiary specialty. *Eur J Hum Genet* 27(4):547–555. <https://doi.org/10.1038/s41431-018-0322-0>
- Schmidtke J, Epplen JT, Glaubitz R, Grimm T, Nippert RP, Tönnies H, Zerres K, Nippert I (2020) Genetic counseling in Germany: development of demand. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 63(9):1161–1167. <https://doi.org/10.1007/s00103-020-03206-8>

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