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# Waste not, want not: Measuring waste and potential clinical risk from limited gatekeeping of Rare Disease genetic testing

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**Abstract**

*Aim*

Review current genetic testing practices to look for evidence of 1) mainstream activity, 2) inappropriate & unnecessary genetic test requests, 3) requests for secondary findings.

*Methods*

Data was extracted from CHI@Crumlin and CHI@Tallaght laboratories databases and analysed.

Searches focussed on 1) quantity of send out requests, 2) evidence of duplicate requests 3) evidence of inappropriate genetic test requests and 4) requests for secondary findings.

We searched both hospital databases to estimate the number of array CGH tests being duplicated unnecessarily.

Total costs of genetic tests were derived from laboratory invoices.

*Results*

11,262 genetic test requests were received in CHI@Crumlin (2022). Mainstream clinicians accounted for a significant numbers of test requests. Requests for secondary findings in minors occurred.

A total of 345 duplicate in-house CHI@Crumlin requests were identified. Gatekeeping of these duplicate samples saved €197,700.

We identified 73/1213 (6%) unnecessary duplicate array tests between CHI @Crumlin and CHI@Tallaght, costing CHI €21,720.

*Discussion*

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Mainstream genetic testing is common. Inadequate gatekeeping results in duplicate and inappropriate testing with significant ethical clinical risk and cost implications. A lack of National governance structures is causing a clinical risk. Our study suggests that these risks are likely to be widespread.

**Introduction**

Genetic testing is distinct from other testing because; 1) these are "once in a lifetime" tests that rarely need repeating, 2) there is a legal requirement for valid consent, 3) results are generally not freely available on hospital systems due to data privacy, 4) samples from relatives are sometimes required to aid result interpretation, 5) the results might have implications for family members, 6) often the test is bespoke for the family and/or individual.

A Department of Clinical Genetics (DCG) at CHI@Crumlin genetic test risk assessment submitted to the Health Service Executive (HSE) in 2010 is currently on the Dublin mid-Leinster risk register[1]. It highlights the risks of inadequate gatekeeping of genetic tests but the report recommendations were never implemented. Since this assessment, next-generation sequencing has become mainstream. Mainstreaming in relation to genetic testing is the term given to the recent practice of medical staff ordering genetic tests independent of Clinical Geneticists. With no diagnostic stewardship at a national level, individual dispatch laboratories are left to absorb these responsibilities, often with limited expertise on the specific requirements.

Nationally, there is no framework to support genetic testing, no test directory to aid test selection, no governance systems enabling service level agreement and/or advising on accreditation status of external laboratories, no system to ensure optimal consent, avoid duplication and cost tests. The absence of a centralised laboratory information management system (LIMS) precludes connectivity and inter-operability between hospitals. Inadequate numbers of clinical and laboratory specialists to guide testing compounds the problem and leads to concerns regarding safe practices and cost efficiency. Additional barriers include data protection rules precluding report access, and whilst confidentiality of sensitive patient data is paramount, not having ready access to a patient's report poses a clinical risk.

Genetic tests are expensive, (Table 1) so it is important to minimise waste. Anecdotally, we had noted evidence of sub-optimal test selection and consent, unnecessary testing duplication as well as limited phenotypic information on test requisitions. We also were aware of inappropriate "add on" testing being ordered by both adult and paediatric

physicians. Examples of inappropriate wasteful add on testing include a gene panel being ordered by one clinician and paid for separately when an exome had been done recently by another clinician. Most other European diagnostic laboratories identify these at receipt and control to optimise the test requested. This is largely absent from Irish hospitals resulting in samples being tested for whatever the clinician requests.

Add on testing also included clinicians ticking a consent box for secondary findings. The definition of a secondary finding (also known as opportunistic genomic screening) is a purposeful search for pathogenic genetic variants unrelated to the reason the patient is being tested, for example a pathogenic variant in an adult onset inherited cardiac gene in a child being investigated for development delay/intellectual disability. Despite European Society of Human Genetic (ESHG) guidelines advising a cautious approach to opportunistic genomic screening, particularly in minors, and the need for pre-and post-test genetic counselling regarding this[2], we have observed a steady flow of referrals requesting counselling for secondary findings (4 in a 6-week 2022 audit). This implies sub-optimal consent of the family as the clinician was unsure how to manage the secondary findings. This is particularly cautioned against in minors as they have no opportunity to understand the possible implications of the test. These events rarely occur within the NHS or European diagnostic laboratory systems as this practice is controlled and differs from the obligations imposed on laboratories in America[2]. Indeed, it is illegal for any laboratory to return secondary findings in France.

In this study, we aimed to review the current landscape of genetic testing, identify current genetic testing levels, evidence of mainstream activity, consent, appropriateness of test requests and occurrence of wasteful unnecessary testing.

**Methods**

Research ethics for this study was obtained from CHI@Crumlin in 2021.

The time periods for data collection differ due to COVID-19 restrictions. The majority of data was collected for the period ending in 2021. We used 2022 to identify the volumes and types of test requests: culture tests eg. karyotype or DNA tests eg. array or panel/exome testing, as this period better reflected the current landscape. Data from 2023 was extracted to identify send out requests for genetic tests to reflect most recent trends.

We reviewed all genetic test requests from CHI@Crumlin from January 2019 - December 2021. Searches on the CHI@Crumlin genetic laboratory databases (iGene and Crumbase)

focused on 1) quantity of send-out requests, 2) evidence of in-house (CHI@Crumlin) duplicate requests 3) evidence of inappropriate genetic test requests and 4) requests for secondary findings. In-house repeat test requests were identified by DCG CHI@Crumlin laboratory. A repeat test was avoided by the laboratory scientist as they were able to identify the previous testing, log the duplicate request and provide the second requesting clinician with a copy of the original test report.

We compared chromosome CGH-array testing between two hospital sites CHI@Crumlin and CHI@Tallaght (January 2017- December 2021), both paediatric sites under the same governance structure, to look for evidence of testing duplication. CHI@Tallaght outsources array testing abroad whereas CHI@Crumlin does in-house testing. The Tallaght sample data was extracted from the TUH Win path LIS using an in-program query and extracted to Excel for further analysis.

Test requests (October-December 2021) for exome analysis to laboratories offering add-on testing were extracted. The appropriateness of additional tests was reviewed using the reference NHS England Genomic Test Directory 2021 as a guide[3]. The shortened time period for this analysis was taken as the work involved a deep dive manual data collection of request forms.

Send out data was derived from more recent records (2023) to accurately identify mainstream activity for two reasons 1) the hospital was back to normal working practice in 2023, (in the post-COVID era), there were still some restrictions in 2022 and 2) anecdotally we had noticed a steady increase in specialists requesting exome testing within the hospital in late 2022.

Total costs of genetic tests were derived from 2023 laboratory invoices.

**Results**

*Genetic test request type and volume (2022):*

The DCG laboratory received 11,262 genetic test sample requests in 2022 of which 4411 were sent abroad for testing, 897 had culture for karyotyping and/or FISH tests and a further 2684 samples were received for chromosome CGH-array testing.

*In-house molecular duplicates (2019-2021):*

A total of n=111 repeat molecular genetic test requests were identified. Fragile X syndrome n=29, Cystic Fibrosis n=15, and Phenylketonuria n=11 were the most common. Notably,

49.5% (n=55) had been reordered by the same clinician, with 57.7% (n=64) from the same hospital. Most repeats were duplicates (n=88, 79.3%) with triplicates also present (n=22, 19.8%). The mean time interval was 41 months, with repeat test requests by the same clinician having shorter intervals than different clinicians (27 v 54 months; p<0.01). Only 84% of Fragile X and 88% of CF samples resulted in a report being issued. In addition to duplications (1.26% for Fragile X and 0.43% CF), samples did not get processed for a variety of reasons (minimal clinical details and/or identification discrepancies), see table 2.

*Cytogenetic duplicates (2019-2021):*

A total of n=234 repeat array test requests were identified equating to 8.7% of samples received. 43.2% (n=101) had been previously ordered by the same clinician. 67.5% (n=158) had been reordered from the same hospital. The majority were duplicates (n=225, 96.2%) with few triplicates (n=9, 3.8%). The mean time interval was 14 months, with repeat test requests by the same clinician having shorter intervals than different clinicians (7 v 19 months; p<0.001).

In summary, a total of 345 duplicate in-house DCG requests were identified and not processed from 2019-2021. Gatekeeping of these duplicate samples alone saved €197,700.

*Exome add-on requests (2019-2021):*

The team was able to identify inappropriate add on requests despite the short time period. 35.5% (n=27/76) of exomes had one or more add-on test. Using the NHS testing directory, 94.4% (n=34/36) were not clinically indicated; of which secondary findings accounted for 73.5% (n=25/34), gene panels 20.6% (n=7/34) and ACMG diagnostics 5.9% (n=2/34). Notably, 51.9% of patients with inappropriate additional tests were minors (n=14/27).

*Array test duplicates (2017-2021)*

We identified 73/1213 (6%) duplicate array tests between CHI@Crumlin and CHI@Tallaght, costing CHI €21,720 during the period. These tests were not identified prior to re-testing because of lack of inter-operability between laboratories despite both part of CHI. The majority (60%) of duplicates were on the Tallaght site.

| Test | UK Laboratories | EU Laboratories |
|---|---|---|
| Test for known familial variant | £200-£250 | €200 |
| Array | £300 | €600-750 (depending on laboratory) |
| Gene Panel | £900 | €1200 |

| | | |
|---|---|---|
| Exome | £1200 | €1500 |
| Trio Exome | £2000 | €2000 |
| Whole Genome | £3000 (trio) | €2500 (singleton) |

*Table 1: cost of common send out genetic tests 2023*

**Comparison 2019 - 2021**

| Year | In / Out | Reports | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All in-house | CF | FraX | BrCa* | Other** in-house | Send out | MIN (includes DNA Bank) | NP |
| **2021** | 6687 / 6284 | 1946 | 1099 | 619 | 67 | 161 | 3242 | 484 | 612 |
| **2020** | 6980 / 7500 | 2160 | 998 | 739 | 174 | 249 | 4156 | 526 | 658 |
| **2019** | 9165 / 9064 | 2889 | 1319 | 938 | 325 | 307 | 4880 | 943 | 352 |

* BrCa sent out from May 2021 onwards

** Other in-house includes: Prader Willi Syndrome, Angelman Syndrome, Spinal Muscular Atrophy, Uniparental Disomy, Irish Traveller mutations, Friedreich Ataxia & Huntington Disease (to May 2021)

MIN = More information needed letters NP = Not processed letters

*Table 2: Volume of some common test requests and number requiring further information prior to proceeding to test (MIN) and numbers that were not processed.*

| Genetic test send out data from DCG CHI@Crumlin | **Clinical Genetics** | **Mainstream** |
|---|---|---|
| Total | 70% test requests | 30% test requests |
| Common send outs below: | | |
| Exomes | 63% | 37% |
| Familial variant testing | 74% | 26% |
| Other (single gene tests, MLPA methylation test, | 65% | 35% |

| | | |
|---|---|---|
| methylation signature test) | | |
| Custom Gene Panels | 52% | 48% |

**Table 3:** Comparison of percentage of send outs for common tests from Clinical Genetics health care professionals versus mainstream clinicians. 2023 was chosen as it provided the most up to date data of mainstream activity.

A detailed analysis of send out data for 2023 showed evidence of a large volume of mainstream activity, see Table 3.


*Figure 1: Roles and responsibilities of Clinical Scientist*

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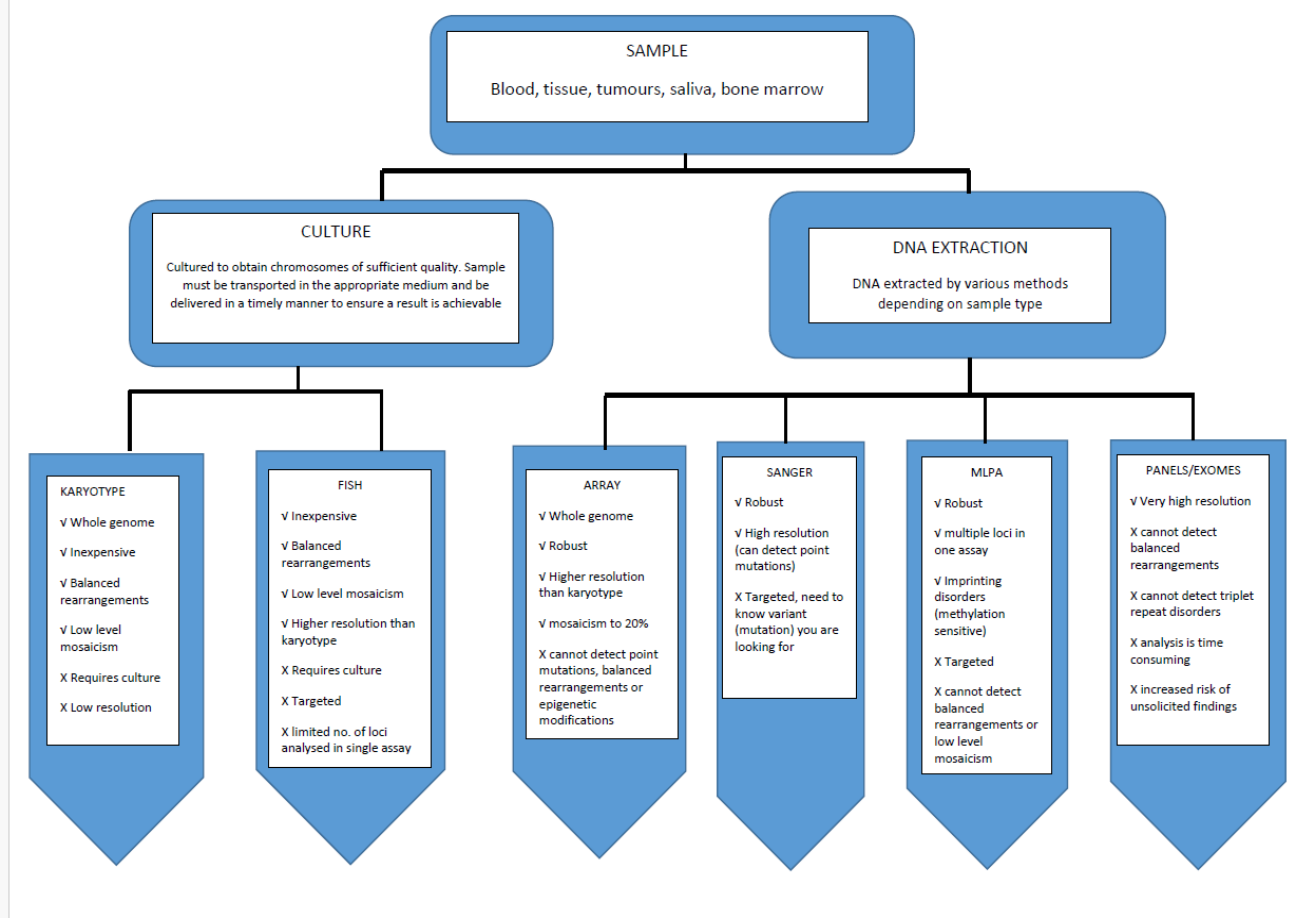


*Figure 2: Complexity of types of genetic testing, some requiring culture, others DNA extraction from different tissues*

## Discussion

Effective stewardship of genetic testing is essential to safely manage a diagnostic laboratory as the genetic toolbox is large[4,5]. Mainstream clinicians cannot be expected to understand the limitations of tests unless they order them regularly. The optimal test may require communication with a Genetics specialist to avoid the wrong test being done[4]. The expert knowledge of experienced Clinical Scientists contributes to safe patient care, their responsibilities are detailed in figure 1. Laboratories face diverse testing requirements depending on the patient group and/or phenotype. Sample culture for karyotyping and FISH (fluorescent in-situ hybridisation) are required by fetal medicine, pathology and paediatric medicine see figure 2. For some chromosomal disorders karyotyping remains the gold standard test. There is currently only one culture laboratory (DCG) in the Irish Republic.

These are time sensitive samples with limited international laboratories offering this service, reinforcing the need to support Irish laboratory services.

Our data shows there is a significant mainstream demand for genetic testing. Comprehensive information about genetic test requests and costs was accessible from the DCG dataset. Although the DCG databases have many limitations, we are not aware of any other laboratory that can trace family samples through the proband's sample. Without correct identification of a familial variant for cascade testing, there is a risk that the wrong variant will be tested or that a generic panel test might be applied at 6 times cost. In addition, DCG does monitor costs of send-out tests and because the largest Clinical Genetics team ordering test is embedded in the same hospital, were able to differentiate requests ordered by Clinical Geneticists versus those ordered by mainstream clinicians.

Most commercial laboratories require minimum data sets including phenotype and confirmation of consent prior to testing. We found evidence of limited phenotypic details and poor test selection by the clinical teams. For example, ordering multiple panel tests where an exome/genome would be more cost effective. Or cases where an exome had been done but a further request for additional panel testing to a different laboratory was made, instead of requesting the original testing laboratory to review the original data, at a much-reduced cost.

Previous publications have shown that deficient IT systems can result in unnecessary testing duplication and that digital intervention is known to help[6-9]. This is particularly relevant in genetics as they are 'once in a lifetime' tests. Published duplication rates include those ranging from 1-7%, very similar to our findings, with up to 32% in others[6-9]. One group noted that only 10.5% of duplicate requests were justifiable, the rest were requested without knowing the test had already been done[9]. Our results mirror this. Some effective online tools to avoid duplication and guide clinicians have been developed[8,9]. Anecdotally, we would estimate that most major teaching hospitals and the fetal medicine/maternity hospitals in Dublin are requesting at least 1000/genetic tests per annum averaging ~€1000 per test. It is possible that the costs of send out tests are reaching anywhere between 10-20 million per annum nationally. If 6% of those tests are being duplicated, a minimum of ~ €600,000-€1.2 million is being wasted within the public sector.

Consent is required prior to genetic testing under the Irish disability act[10] and is of particular relevance when testing minors for adult onset disorders[11]. We have anecdotal evidence of sub-optimal consent, where referring physicians have admitted not being aware they had consented patients to secondary findings following identification of one. Commercial

laboratories use simple tick boxes to indicate consent for secondary finding was taken, however, it is unclear what information the patient has been given as part of the process. In addition to the ESHG's position statement on opportunistic genomic screening[2,12]; the Royal College of Physicians in London have published best practice guidance on testing of minors[12] and ethical issues in prenatal genetic diagnosis[13,14]. This considers genetic testing in children for adult-onset conditions where no medical or risk-reducing intervention is possible to be unethical. This highlights a clinical risk; as a patient presenting with a specific clinical issue can receive a result with significant clinical and reproductive implications without fully informed consent and, in the case of minors, without any consent.

Our findings show lack of visibility of genetic test results for clinicians practising within the same hospital preventing ready clinician access to results. Contradictory pressures exist; 1) the need to protect sensitive genetic test reports to comply with data protection versus 2) the need for clinicians to access patient reports to ensure best practice. Without a centralised LIMS, this will not be achievable. Results of predictive tests are highly sensitive and strict controls and rights access need to be observed to ensure privacy and adherence to ISO 9001 4.2(confidentiality), 6.2.3 (Authorization), 6.3.2 (Facility controls) and 7.4.1.2 (Result review and release). The American College of Medical Genetics has published guidance on best practice for access and privacy when integrating genomic data into electronic health care records (EHR)[15,16], with a follow-up study on integration in practice[17]. Currently, no Irish hospital can integrate genomic data into electronic healthcare records and indeed few have EHR in operation. It rests on individual laboratories to control requests for access to reports, a highly onerous process.

We suggest a solution via investment in a fit for purpose national LIMS system with an online portal. Whilst logging a test request, minimum parameters for testing e.g. phenotype, consent, terms and conditions/limitations, and alert to possible duplication would occur. Appropriately administered permissions and safeguards could be embedded as well as a simple educational tool within which would support clinicians and optimise safe ethical practices. Repatriation of testing to a national public laboratory service should be considered as it's likely to be cost saving and the genetic data would be maintained in Ireland (the importance of this is huge and impossible to quantify). This would allow accurate testing of relatives as the familial variant could be verified by easy access to reports and samples from affected individuals used as positive controls. It would also facilitate variant interpretation as diagnostic scientists could check if a variant, that might not appear on international healthy human databases, was found commonly in the Irish population.

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The current testing landscape poses a clinical risk for a number of reasons. Clinician time is spent chasing reports from multiple international laboratories, time that would be better spent on patient care. Accessing reports on patients and/or the parents is very difficult as IT systems are inadequate. This means clinical genetic teams are being asked to counsel patients and clinicians are being asked to manage patients without access to all relevant reports. If a clinician is on leave, it can be very difficult for their deputy to access reports from international laboratories when one is not the requesting physician. There is limited audit trail for many samples leaving the country for testing. Some hospitals still record the send out request in handwritten logbooks. Some time-sensitive culture requests (including many antenatal testing) are now sent abroad increasing the risk of test failure if the sample is delayed. Parental sample requests are not linked to the probands requests (apart from CHI@Crumlin) leading to risks of the results not linking back to the child's report precluding full interpretation of the child's genetic findings. The lack of timely access to clinical genetic expertise means clinicians are being asked to interpret complex genetic test reports without specialty back up. The lack of national gatekeeping means inappropriate and duplicate testing is commonplace. This causes confusion for both patient and clinician as the patient is aware some testing is done but often unable to accurately describe which test was ordered by another Doctor, and the report is not retrievable.

**Discussion**

Currently, Irish clinicians and scientists are working in a systemic high-risk environment. Inadequate gatekeeping results in duplicate and inappropriate testing with significant ethical clinical risk and cost implications. A lack of diagnostic stewardship is evident and the lack of governance structures suggest that these risks are widespread. We hope that these finding will inform the implementation of the National Genetic and Genomic Strategy and ensure that patient safety is priority by development of a centralised well-supported genetic testing laboratory service.

**Declarations of Conflicts of Interest:**
We acknowledge the Adelaide Health Foundation for supporting this research project.

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