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ARTICLE

Evaluating the resource implications of different service delivery models for offering additional genomic findings

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PURPOSE: To evaluate the resource implications of different delivery models for the provision of additional findings (AF) in genomics from a health-care purchaser perspective.
METHODS: Data from the Additional Findings study were used to develop and validate a discrete event simulation model that represented the pathway of delivering AF. Resource implications were estimated by microcosting the consultations, sample verifications, bioinformatics, curation, and multidisciplinary case review meetings. A proof-of-concept model was used to generate costing, and then the simulation model was varied to assess the impact of an automated analysis pipeline, use of telehealth consultation, full automation with electronic decision support, and prioritizing case review for cases with pathogenic variants.
RESULTS: For the proof-of-concept delivery model, the average total cost to report AF was US$430 per patient irrespective of result pathogenicity (95% confidence interval [CI] US$375–US$489). However, the cost of per AF diagnosis was US$4349 (95% CI US $3794–US$4953). Alternative approaches to genetic counseling (telehealth, decision support materials) and to multidisciplinary case review (pathogenic AF cases only) lowered the total per patient cost of AF analysis and reporting by 41–51%.
CONCLUSION: Resources required to provide AF can be reduced substantially by implementing alternative approaches to counseling and multidisciplinary case review.

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INTRODUCTION

Given the rising prominence of genomic sequencing in health care, there has been extensive debate among medical and research communities, patients, and service providers about the policies and practices regarding additional findings (AF) in medical genetics. AF analysis refers to the deliberate and intentional search for clinically significant variants unrelated to the primary reason for genomic sequencing but that may have improved patient outcomes through earlier identification and management.[1–3] Although the term "secondary" findings is also used in the genomics literature, here the term "AF" is adopted consistent with patient preferences.[2] A need for clear guidance for the management of AF in the United States led to the initial 2013 American College of Medical Genetics and Genomics (ACMG) recommendations that called for the identification of pathogenic variants from a defined minimum list of genes performed and returned to all patients having genomic sequencing.[4] In response to criticism concerning the different uses of genomic sequencing, mixed experiences in facilitating and supporting informed decision making, and the lack of strong evidence to support both the predictive value impact of AF, the ACMG recommendations have undergone numerous revisions.[5–9] However, unlike the United States, most countries do not have national policies supporting return of AF in clinical practice and have not benefitted from a long learning process from routine implementation.[10,11]

A challenge regarding the routine provision of AF is that the economic consequences of AF for health systems are still largely unknown.[12] Economic evaluations for detecting variants from the ACMG recommended gene list have focused on only a subset of genes from the ACMG list or on targeted, high risk populations.[12] Though reporting AF is likely cost-effective for certain patient population groups, substantial additional data on the benefits, risks, and cost of analysis and return of AF are required to formally evaluate the economic impact of offering AF to patients when genomic sequencing is used in clinical practice, and appraise the "value for money" of AF to decision makers.[13–15] In doing so, considerations should be given to the possibilities to act preventively or intervene based on AF, while also recognizing potential harms for both the patient and health-care system from overdiagnosis and overutilization of health-care resources to manage these findings.[16–18]

Should national policies support the provision of AF testing, evidence is needed to guide how this should be achieved while accounting for the financial impact of the service.[19,20] While laboratories in the United States have adopted a model whereby genetic counseling and analysis related to AF occur alongside diagnostic testing, a range of alternative approaches to counsel, curate, and disclose AF can be taken.[3] Without clear guidance, provision of AF has not been adopted consistently in clinical care by laboratories in other countries, and those laboratories that are actively returning these findings to patients have inconsistent practices.[10,18,21] For policy makers and service providers developing protocols for delivery of AF, a major source of concern has been a lack of available evidence regarding the capital and labor health-care resources required for AF.[5,6,8,21] Different service designs have different resource implications, and accordingly determine the cost to provide AF to patients and the

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overall feasibility of the service from a provider perspective. Investigating several separate models for service delivery of AF is required to provide the necessary information for implementing an effective service tailored to patients' preferences while minimizing organizational burden and reducing costs. These studies are needed to inform future policy deliberations on the cost-effectiveness of AF.

To understand the workflow for delivering AF to patients after completion of primary diagnostic testing, this study aimed to estimate the resource implications of different service delivery models through a microcosting analysis. In achieving this objective, data were collected from an AF "proof-of-concept" service whereby patients were offered reanalysis of their exome sequencing (ES) data after completion of primary diagnostic testing. Data were used to populate a discrete event simulation (DES) representing alternative service designs considered relevant by involved stakeholders.

MATERIALS AND METHODS

Additional Findings study and data collection

This study was part of the Melbourne Genomics Health Alliance program and received Human Research Ethics Committee approval (13/MH/326). All participants from the Additional Findings study provided written informed consent prior to the current study. Those who proceeded with reanalysis of the data for AF also provided clinical consent.

The Additional Findings study was conducted to evaluate a novel two-step model of care based on a traditional predictive genetic testing service. A "proof-of-concept" AF service was established and tested with people who had completed primary diagnostic testing using ES with analysis limited to genes based on the patient's clinical condition.[3] Inclusion criteria for the Additional Findings study were adults aged 18 years or older who had already received results of their clinical diagnostic exome test and had participated in an overarching study evaluating clinical genomic testing at participating tertiary-level hospital in Melbourne, Victoria, Australia. If patients agreed to AF analysis, reanalysis of the patient's stored data were conducted at the Victorian Clinical Genetics Service (VCGS) with analysis restricted to variants within a predetermined list of 58 genes associated with clinically actionable, adult-onset conditions. This list was similar to the ACMG SF v2.0 genes list with a few exceptions for genes and conditions typically occurring in children.[22] Further details of study recruitment and the selection of the AF genes list have been described elsewhere.[3] Data pertaining to management during patient involvement in the study were extracted including detailed data on resources utilized, dates and duration of clinical activities, and outcome of AF analysis.

AF service provision workflow in the Additional Findings Study

Figure 1 shows a flowchart representing the AF service provision pathway that was used for the Additional Findings Study, which will be referred to as the proof-of-concept delivery model.

This delivery model is broadly divided into five clinical stages: consent process, variant curation, multidisciplinary case review, reporting, and disclosure. The *consent process* consisted of a pretest genetic counseling appointment whereby patients explored the options of accepting or declining AF with a genetic counselor. If patients decided to proceed with AF and gave (clinical) consent, stored clinical genomic data were extracted for reanalysis. *Variant curation* first involved a sample identification check performed by a medical scientist for all genomic data where diagnostic sequencing had been performed at an external laboratory to ensure retrieved genomic data correctly belonged to the patient. Participant genomic data were then passed through a bioinformatic pipeline analysis, and from that point a medical scientist manually curated identified variants to assess available evidence in determining pathogenicity classification of a particular variant. The initial variant classifications were discussed at a *multidisciplinary case review* meeting and consisted of a quorum of a genetic counselor, clinical geneticist, medical specialist, senior medical scientist, and three medical scientists. Members of the multidisciplinary case review meeting agreed which variants should undergo full curation and/or made recommendations of variants for curation for individual patient cases if further curation of (additional) variants and a second review meeting were requested. Pathogenic or likely pathogenic variants were considered as an AF result. In *reporting*, when an AF was identified, a confirmatory testing on a second sample was conducted as per laboratory protocol for predictive genetic testing. A clinical test report was prepared by a medical scientist for all patients before approval by a senior medical scientist test and release to the requesting practitioner. *Disclosure* of AF to patients was done in person by a genetic counselor and/or clinical geneticist with review by other medical specialists as required. If no AF was identified, the negative result was returned to patients by a genetic counselor, typically over the phone.

Alternative AF delivery models

In exploring opportunities to enhance service access and efficiency of delivering AF, three hypothetical alternative delivery models were defined based on input from clinical and laboratory experts including clinical geneticists, genetic counselors, medical scientists, and health services researchers. Alternative AF delivery models were suggested to enhance the operational workflow for AF reporting based on the experiences of stakeholders taking into account how these changes could improve the financial cost of an AF service. Discussion to define alternative models was an interactive process until consensus was reached. In particular, changes were made to the proof-of-concept delivery model, and labeled as the (1) In-person model, (2) Telehealth model, and (3) Automated model. Proposed changes to the proof-of-concept delivery model, which result in the alternative delivery models, are summarized in Fig. 1 and separate graphical illustrations outlining the workflow of each alternative delivery model are presented in the Supplementary Figs. S1–S3.

In-person model. The In-person model was defined to test the resource implications of alternative variant curation procedures, as they arose from experiences with the proof-of-concept AF service. As such, this delivery model was designed to reflect laboratory operations more consistent with screening tests including streamlining variant detection and adjusting case priority for multidisciplinary review. Therefore, the following changes were tested and compared with the proof-of-concept delivery model: removal of the sample identification check, automation of the bioinformatic pipeline analysis and curation (with a manual check of automated curation) to reduce involvement from medical scientists, multidisciplinary case review meetings to only review likely or likely pathogenic AF variants, and removal of any further curation and multidisciplinary case review meetings.

Telehealth model. The Telehealth model was proposed to replace in-person genetic counseling appointments for AF. The purpose of this delivery change was to address barriers to service access. The Telehealth model retained the same changes to laboratory operations as the in-person model, but genetic counseling appointments during consent and disclosure were via telehealth. However, disclosure of pathogenic AF remained as an in-person appointment with a genetic counselor and clinical geneticist. Taking into account that genetic counseling appointments through telecommunication technologies are on average shorter than an in-person appointment,[23] we adjusted the duration of this clinical activity pre- and post-test (only for patients without AF) by applying multiplicative scale factor from reported literature to the data.

Automated model. The Automated model assumed an alternative approach to informing patients about the option of AF and supporting them to make decisions, such as decision support materials. In this model, disclosure of AF results uses electronic communication platforms (e.g., emails or online website portal).[24] This delivery model, like the Telehealth model, targeted changes to consent and disclosure, but considered alternative communication strategies to ease the burden on clinical services to support consultations about AF. It was assumed that 90% of people using this model would make use of decision support materials to make a decision about receiving AF. It was assumed that 10% would require assistance from a genetic counselor to make a decision about AF analysis. In-person post-test genetic counseling was required if an AF was identified, but patients without AF received their results electronically, with the assumption that post-test genetic counseling was also made available to 10% of patients without AF to discuss results further.

Micro-costing analysis

The resource implications of the different delivery models were estimated by performing a microcosting analysis using the Additional Findings

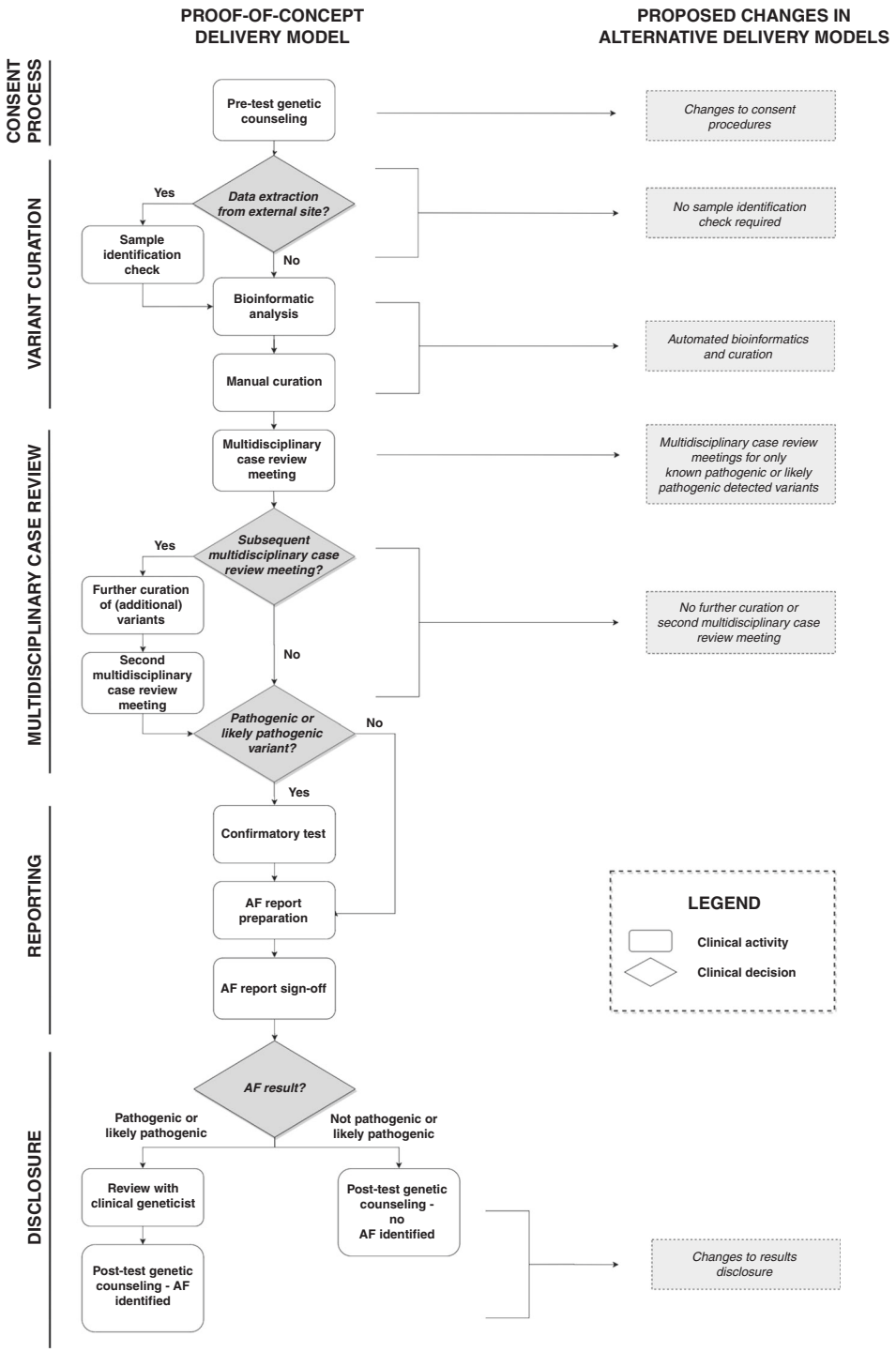

Fig. 1 Additional findings (AF) delivery model structure. The proof-of-concept delivery model flowchart represents the clnical processes involved to analyze and return AF to patients. Several proposed changes were made to the proof-of-concept delivery model in order to estimate the cost of alternative AF delivery models. AF additional findings.

study data. The micro-costing analysis was a direct enumeration of resources consumed for simulated patients in the simulation (see next section) and the unit cost to consume resources following bottom-up costing methodologies. This included analysis of the amount and type of staff involved and the amount of time they spent on a particular task, as well as the important events and the timing between these events. The health-care purchaser perspective was adopted for the micro-costing analysis to estimate the cost arising from the service, and hence only direct medical costs related to the provision of AF were included (i.e., cost of consumables to analyze AF and cost of health-care labor relevant to clinical activities needed to curate and discuss AF). Out-of-pocket expenses, travel costs for patients and/or families, overhead costs, and other related costs were not considered. Unit costs of consumables and health-care labor were acquired from testing laboratories and state government and are listed in Table 1.[25,26] All costs were expressed in 2020 dollars (USD) and an exchange rate of $1 USD = $0.69 AUD was applied in our study (7 January 2020).

Table 1. Cost input parameters to microcosting analysis.

	Cost	Reference
Sample identification check (cost per sample)	$505.20	Existing data
Bioinformatic analysis (cost per sample)	$64.95	Existing data
Confirmatory test (cost per sample)	$144.34	Existing data
Clinical geneticist (hourly cost)	$93.49	Medical Practitioners Award[26]
Genetic counselor (hourly cost)	$64.80	Victorian Public Health Sector Enterprise Agreement[25]
Laboratory manager (hourly cost)	$83.36	Victorian Public Health Sector Enterprise Agreement[25]
Medical scientist (hourly cost)	$61.75	Victorian Public Health Sector Enterprise Agreement[25]
Medical specialist (hourly cost)	$93.49	Medical Practitioners Award[26]

Discrete event simulation

To investigate the resource impact of AF, all four delivery models were implemented in a DES constructed using the `simmer` package in R.[27] DES is an advanced simulation modeling technique in operational and health services research for simulating individual patient pathways in a system.[28] This modeling methodology can be used to evaluate and optimize existing and hypothetical processes, and therefore provides an efficient and ethical approach to evaluating several service designs. In our study, data from the Additional Findings study was used to define and simulate a patient population that are having AF reported according to a specific delivery model to understand the extent of resource consumption, and how this translates into a financial cost for the service. Competing access for resources was not considered in this simulation, and therefore there were no capacity limitations to resources in the simulation. This study was developed in alignment with good research practices in health-care DES modeling.[28] For detailed information, please see Supplementary Materials and Methods.

A full list of attributes and input parameters is available in Supplementary Table S1. Duration of clinical activities and time-to-event parameters were modeled in the simulation by examining four parametric distribution types appropriate for modeling durations and time-to-events: Weibull, Weibull Mixture, Gamma, and Log-Normal.[29] These were fitted on the data through maximum likelihood estimation using the `fitdistrplus` and `mixtools` packages in R.[30,31] The best-fitting distribution was selected according to goodness-of-fit based on visual inspection of density plots, quantile–quantile plots and percentile–percentile plots. In case visual inspection did not identify a clear best-fitting distribution, quantitative measures from the Akaike information criterion and Bayesian information criterion were additionally considered (see Supplementary Table S2 for details). For input parameters where multimodality was present, a Weibull mixture distribution was chosen. If no patient-level data was available for clinical activities, a Weibull distribution was estimated following the method of moments based on an assumed mean and standard deviation obtained from expert opinions. This simulation was validated through regular meetings with relevant experts to discuss credibility and plausibility of simulation structure and outputs. In terms of internal validity, accuracy of mean estimates of the probability distributions for duration of activities and time-to-event parameters were compared with the original data.

Probabilistic analysis assessed the uncertainty in the simulated outcomes arising from the uncertainty in the input parameters. For parameters informed by individual patient data from the Additional Findings study, a bootstrapping approach was used to obtain correlated sets of input parameters.[32] Where no individual patient data were available, parametric distributions reflected uncertainty and provided in Supplementary Table S1. The probabilistic analysis was performed by evaluating the simulation for 5000 different sets of input parameters, simulating 10,000 patients per service design in each evaluation. Outcomes of the probabilistic analysis were summarized by their mean and corresponding 95% confidence interval (CI).

RESULTS

The results of the proof-of-concept delivery model showed that the average time spent on curating and reporting AF overall was 240 minutes per patient (95% CI: 207–275) (Table 2). Manual curation took the most time to perform, consuming an average time of 85 minutes per patient, which was 35% of the average total time to report AF to patients. For patients who ultimately were reported as having AF, the average time was 280 minutes per patient (95% CI: 246–317). This was longer than patients where no AF was reported at an estimated average time of 239 minutes per patient (95% CI: 210–271). These differences were due to additional time spent on reviewing patient cases with AF, and longer post-test genetic counseling appointments for patients with AF compared with patients without AF. Otherwise, the average time of all other clinical activities was similar.

The average total cost to test for providing AF was $430 per patient (95% CI $375–$489) (Table 2). The majority of this cost was attributable to activities within the variant curation and amounted to $190 (44%) of the average total cost in the proof-of-concept delivery model. This was then followed by the cost of reporting ($109; 25%) and case review ($60; 14%). Comparing between subgroups, the average total cost for patients with AF was $1001 per patient (95% CI $946–$1058), which was more expensive than patients without AF at an average total cost of $367 per patient (95% CI $333–$403). Factors contributing to this variation in cost included additional confirmatory tests and patient case reviews with a clinical geneticist required for patients with AF as well as longer post-test genetic counseling appointments as opposed to patients without, as stated above. These activities predominately occurred within the multidisciplinary case review and disclosure stages of the proof-of-concept delivery model, as different tasks are required to examine and return a clinically actionable finding to patients compared with cases where no pathogenic variants were identified.

The AF proof-of-concept service identified AF in 8 of 81 (10%) of patients analyzed. Accordingly, the average total cost to the health-care purchaser for identifying one patient with AF was $4349 (95% CI $3794–$4953) (Table 2).

Comparing the simulation results of all delivery models, the Automated model was the most efficient service model with an average total cost of $210 per patient (95% CI $169–$258), which cost 51% less than the proof-of-concept model (Table 3). This was followed by the Telehealth model at $236 per patient (95% CI $195–$285) resulting in a 45% cost reduction compared with the proof-of-concept model. Finally, the average total cost of the In-person model was $253 per patient (95% CI $212–$301) and was 41% less costly than the proof-of-concept model. Cost improvements were driven by automated bioinformatic and curation analysis, and reduced labor time owing from utilizing other modes of communications such as telehealth, online communications, and decision support materials rather than in-person appointments and from prioritizing case reviews to patients with AF only (Fig. 2). These changes are evident across all clinical stages in the AF service provision except for reporting as the process to report AF to patients was consistent across all alternative AF delivery models.

Table 2. Mean estimated outcomes for the proof-of-concept delivery model.

	No AF identified		AF identified		Total	
	Time per patient, minutes (%)	Average cost per patient, $ (%)	Time per patient, minutes (%)	Average cost per patient, $ (%)	Time per patient, minutes (%)	Average cost per patient, $ (%)
Consent process						
Pretest genetic counseling	40 (17)	43 (12)	40 (14)	43 (4)	40 (17)	43 (10)
Total	40 (17)	43 (12)	40 (14)	43 (4)	40 (17)	43 (10)
Variant curation						
Sample identification check[a]		37 (10)		37 (4)		37 (9)
Bioinformatic analysis[a]		65 (18)		65 (6)		65 (15)
Manual curation	85 (36)	87 (24)	85 (30)	87 (9)	85 (35)	87 (20)
Total	85 (36)	190 (52)	85 (30)	190 (19)	85 (35)	190 (44)
Multidisciplinary case review						
Multidisciplinary case review meeting	38 (16)	47 (13)	38 (13)	47 (5)	35 (14)	47 (11)
Further curation of (additional) variants	9 (4)	9 (2)	9 (3)	9 (1)	9 (4)	9 (2)
Second multidisciplinary case review meeting	4 (2)	5 (1)	4 (1)	5 (0)	4 (2)	5 (1)
Total	50 (21)	60 (16)	50 (18)	60 (6)	47 (20)	60 (14)
Reporting						
Confirmatory test[a]				505 (50)		50 (12)
AF report preparation	30 (13)	31 (8)	30 (11)	31 (3)	30 (13)	31 (7)
AF report signoff	20 (8)	28 (8)	20 (7)	28 (3)	20 (8)	28 (6)
Total	50 (21)	59 (16)	50 (18)	564 (56)	50 (21)	109 (25)
Disclosure						
Review with clinical geneticist			20 (7)	53 (5)	2 (1)	5 (1)
Post-test genetic counseling	14 (6)	15 (4)	35 (13)	92 (9)	16 (7)	23 (5)
Total	14 (6)	15 (4)	55 (20)	145 (14)	18 (8)	28 (7)
Average total time per patient, minutes (95% CI)	239 (210–271)		280 (246–317)		240 (207–275)	
Average total cost per patient, $ (95% CI)	367 (333–403)		1001 (946–1058)		430 (375–489)	
Average total cost of AF diagnosis, $ (95% CI)					4349 (3794–4953)	

Estimates are subjected to rounding errors.
AF additional findings, *CI* confidence interval.
[a]Hands-on time was not recorded in the simulation modeling as the costs for these clinical activities were based on cost per case.

Patients with AF remained more expensive than patients without AF in all alternative hypothetical models.

DISCUSSION

This study investigated the resource implications of reporting AF according to several delivery models through a simulation model developed based on data from the Additional Findings study. The results demonstrated that the estimated average total cost to identify a single patient with a clinically significant AF was $4349. Automating bioinformatic and curation pipeline analysis and altering approaches to how patients are clinically reviewed and counseled can make the AF genetic service more financially feasible. In particular, alternatives to in-person consultations and multidisciplinary case review meetings and in-person post-test genetic counseling appointments for only cases with pathogenic AF contributed to reducing service cost.

The health economic impact of genomic sequencing as a diagnostic test has been previously examined across multiple clinical indications.[33–35] Far fewer studies have reported whether or not the additional benefits of screening additional genetic information outweigh the harms and costs to assess genes on a defined list of genes.[20,36] The real-world experience of AF analysis has focused on several practical issues for laboratories and clinical services who have adopted or in the progress of adopting AF reporting.[7,15,21] These challenges include time-intensive clinical activities arising from the interpretation of pathogenicity of individual variants coupled with complex logistical system

restraints and increased workloads that may interfere with tests for primary diagnostics. Genetic counseling for AF can also be difficult because of the emphasis on risk management and prevention of conditions for which patients may have no experiential understanding, as opposed to a clinical diagnosis of an apparent condition. This distinction should be adequately expressed to patients engaged with the AF service. These practical issues for laboratories and clinical services contribute to a financial cost and influence the adoption of AF into clinical practice.[5] More specifically, the cost of opportunistic screening may limit access to the service, depending on whether those costs are reimbursed or patients must pay out-of-pocket.

Table 3. Average total cost of alternative delivery models for AF.

	Average total cost per patient, $ (95% CI)	% Difference compared with proof-of-concept model
Proof-of-concept model		
No AF identified	367 (333–403)	
AF identified	1002 (945–1,058)	
Total	430 (375–489)	
Internal model		
No AF identified	182 (176–187)	−50.4
AF identified	895 (853–937)	−10.7
Total	253 (212–301)	−41.2
Telehealth model		
No AF identified	165 (161–168)	−55.1
AF identified	883 (841–926)	−11.9
Total	236 (195–285)	−45.1
Automated model		
No AF identified	139 (136–143)	−62.1
AF identified	855 (813–897)	−14.7
Total	210 (169–258)	−51.1

AF additional findings, *CI* confidence interval.

In an effort to minimize the cost of analysis, our results suggest design of new clinical services for the identification of AF should consider automating the bioinformatic and curation analysis, and implementing multidisciplinary case review and disclosure procedures conditional on whether an AF is identified following curation. Offering AF within a single institution was also less costly than reanalyzing genomic data that have been stored externally, which also mandates assessment of legal and ethical risks surrounding issues of sharing and reanalysis of clinical data.[37] Where AF analysis does not occur concurrently with diagnostic testing, the source of the data to be reanalyzed is therefore an important consideration. This should align with national and regional legislation and cultural norms with regard to data sharing, but jurisdictional health systems, infrastructures, and expertise may affect the overall cost.[5,11] Furthermore, adapting counseling to include the options of telehealth and electronic communications during pre-test counseling and post-test counseling for patients where no AF was found will reduce the cost. By understanding critical areas within the service design that drive the cost of AF and addressing these concerns through service design, these solutions provide a health service perspective into optimal resource utilization and reporting strategies, as well as reducing uncertainty around the resources needed to operate such a service.

Other considerations for service design of AF include potential psychosocial impact associated with receiving additional genetic information on patients and/or family members.[6,38,39] Patient preferences regarding telehealth and decision support materials should also be taken into account. Previous research has indicated that these modes of communications are acceptable in ensuring and supporting patient choice while maintaining a high satisfaction from patients.[24,40] Though more research is needed to validate the acceptability of alternative counseling schemes for AF, especially for communication through emails or online website portals, these platforms do offer opportunities for wider access of the AF genetic service. Practical restraints should also be examined especially for an automated pipeline as the quality of the pipeline will depend on data availability for variant penetrance and significance. The cost of diagnosing or identifying a single

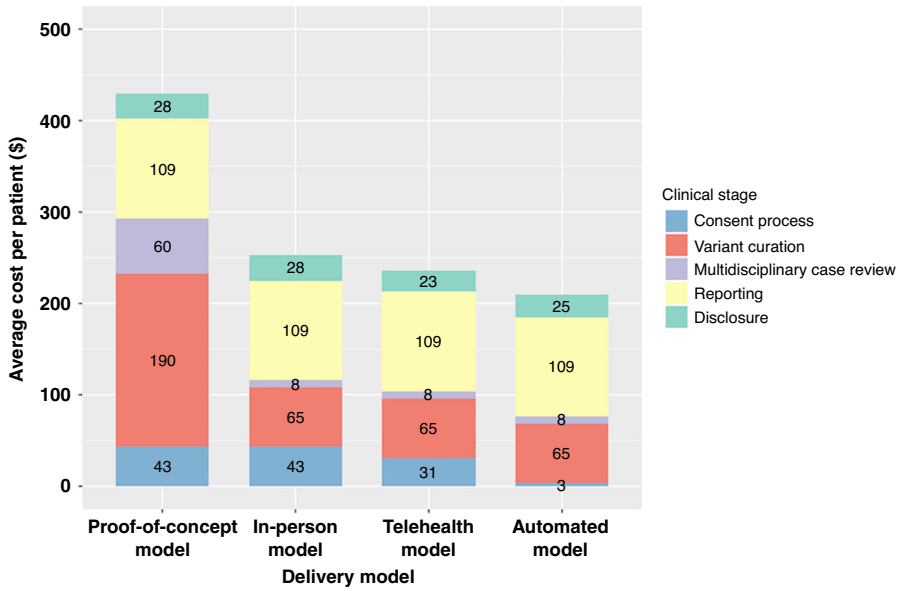

Fig. 2 Average total costs of additional findings delivery models categorized into clinical stages.

patient with AF will also be influenced by the prevalence of pathogenic variants of conditions implicated in the gene list within a population, and a higher prevalence is likely to result in greater costs due to greater workload on the service.[41] Finally, focus here was on reanalysis of data from ES. Genome sequencing (GS) is increasingly used and provide more data than ES; however, it is unlikely that the number of extra AF identified using GS would be significantly higher than ES in the near future. The analysis for both would be performed on the same defined list of genes, and most of the additional data from GS test is not currently interpretable with respect to human disease.

There are certain limitations to this study. Firstly, the micro-costing estimated the cost of the service delivery models in its prototyped form and does not include startup expenses to train and prepare the workforce to offer AF to patients or to setup automated pipelines. The analysis also did not incorporate costs of genomic sequencing and genomic data storage as these costs do not arise specifically in relation to the analysis of AF but rather are borne from primary diagnostic sequencing. Secondly, we did not measure the long-term consequences or assess health-care utilization following disclosure of AF result. This information would have provided a better understanding of the downstream health-care expenditure from clinically actionable AF, but previous studies in the United States have suggested that the observed cost of medical action a year after results was returned was modest at an average cost of $128.[42] This suggests that in the short-term, offering analysis for AF does not adversely affect health-care spending on the relatively low number of patients where AF were found, but the implications of AF on future clinical management need to be examined. Such studies should also include patient health outcomes for a better understanding of the value of AF to the health system. Lastly, this simulation made several assumptions pertaining to parameters of key inputs when patient-level data were not available, and assumed a complete uptake of AF analysis by those who engaged with the service. Clinical and laboratory experts were directly consulted to define the parameters based on their experiences in clinical genetics and the proof-of-concept AF service. More studies with real-world data are needed to validate our findings and to cost the concurrent model of AF analysis, where AF testing occurs together with diagnostic testing, currently applied by some laboratories around the world. The advantage of our DES model is that it provided a tool for decision makers to appraise the most effective use of health-care resources by experimenting with alternative simulation scenarios that would not otherwise be possible.

Conclusion

Implementing AF in routine care requires further investigation of optimal service delivery models. This study used a dynamic modeling framework to compare three alternative delivery models to a proof-of-concept model used in the Additional Findings study. In the proof-of-concept model, the average total cost to report AF in patients was $430 per patient, resulting in an average cost to diagnose a single patient with AF of $4349. The analysis of alternative delivery models demonstrates that the cost of the service can be reduced by 40–51% by implementing an automated pipeline for AF, giving precedence to clinically significant variants in multidisciplinary case reviews and reporting, and adopting telehealth and other evidence-based communication platforms. This information can assist in the development of future AF policies and service designs and ease the burden for service providers as they manage AF in their own clinical practice.

DATA AVAILABILITY

All model inputs used in this study are described or included in this article and the electronic supplementary information.

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Conceptualization: M.V., K.D., M.M., E.L., B.C., C.G., M.I.J.; Data curation: M.M., E.L., B.C., C.G.; Formal analysis: M.V., K.D.; Funding acquisition: C.G., M.I.J.; Methodology: M.V., K.D., M.I.J.; Software: M.V., K.D.; Supervision: K.D., M.M., C.G., M.I.J.; Visualization: M.V.; Writing – original draft: M.V.; Writing – reviewing & editing: M.V., K.D., M.M., E.L., B.C., C.G., M.I.J.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS DECLARATION

This study was part of the Melbourne Genomics Health Alliance program and received Human Research Ethics Committee approval (13/MH/326). All participants from the Additional Findings Study provided written informed consent prior to the current study. Those that proceeded with reanalysis of the data for AF also provided clinical consent.

ADDITIONAL INFORMATION

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