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Leveraging complexity features in Genomic Implementation

CHRIS WORKING PAPER #102

FROM THE AUSTRALIAN INSTITUTE OF HEALTH INNOVATION

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Leveraging features of complexity to drive implementation: a critical review of studies from clinical genomics

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Background

The use of complexity theory in health services research is an emerging field in which the health system is viewed as a complex adaptive system.[1, 2] Complex adaptive systems (CASs) have distinct characteristics: they are made up of components (e.g., cells, animals, computers, people), and are multifaceted, often hierarchical, dynamic, and interactive, with the actions of one component affecting the context in which other components act.[2] Complex adaptive systems are characterised by dynamic, non-linear interactions making changes hard to predict. Behaviours in CASs are emergent rather than forecastable, and feedback and incentives rather than top-down instructions stimulate change. Human CASs show the added dimension of social processes, with self-organisation and interaction driven by sense-making[3] among the semi-autonomous agents. Health systems fit this model well with their large numbers of interacting health professionals, multifaceted departments and specialties, self-organising teams, and social processes.

The introduction of genomic medicine into already complex and resource-stretched clinical contexts calls for an exploration of these characteristics of complexity to identify possible leverage points – places in complex systems where a small shift can lead to fundamental change in the system as a whole – that can foster sustainable adoption. Genomic medicine – which we define as the sequencing of exome, genome or large gene panels– is potentially paradigm shifting for clinical practice and patient outcomes, and requires extensive investment in new infrastructure, specialised expertise and training, attention to ethical and legal implications, new ways to manage data, fresh approaches to privacy and workforce considerations. It carries huge potential to improve health outcomes by providing diagnoses for previously unexplained genetic conditions,[4, 5] guiding treatment and management decisions,[6] and informing risk management strategies into the future.[7] Many countries are moving closer to implementation of genomic testing into routine clinical care.[8] The routinisation of genomic medicine provides a rich field to explore how complexity science can inform implementation endeavours. This approach has been used to design interventions in other areas of health care.[9]

In this working paper we report on a review of selected peer-reviewed papers on implementation of genomics in clinical practice. These studies were purposively selected from a larger systematic review (paper in preparation). All selected articles were set in real-world situations and had enough detail of the context to say they had taken a CAS perspective. Our research questions for the papers were: (1) What characteristics of a CAS can we identify in these papers? (2) Can these identified characteristics be used to leverage sustainable adoption, or avoid pitfalls? (3) How can complexity science inform genomic implementation?

Methods

The set of 14 articles that were the focus of our critical review came from a larger systemic review [paper in preparation] that followed PRISMA [10] guidelines.

Analysis

We used a list of the characteristics of CASs derived from the literature[2, 9, 11-13] as a framework to search for evidence of these characteristics in each of the included articles. Each article was assessed for evidence of agents' learning, adapting or sensemaking, instances of interdependencies, feedback loops, interconnections, self-organisation or emergence of new behaviours, or for examples of non-linear, uncertain or unpredictable processes. This was done by two authors (JL, KC) and then discussed with all authors.

Synthesis

Articles were further analysed to identify any points that could be leveraged or that needed to be addressed (e.g., pitfalls to be avoided). Finally, we synthesised results to make recommendations on how to leverage complexity characteristics in implementation of clinical genomics efforts.

Results

All 14 articles showed evidence of CAS features (see Table 1). Deductive reasoning was used to identify leverage points and was considered to have occurred when CAS features had been directly used in some way to achieve change. Leverage was achieved by: employing an active, fluid response to learning and sensemaking; taking into account unpredictable outcomes and uncertainties; building on self-organisation and emergent behaviours (often driven in the first instance by sensemaking); and recognition and management of interdependencies.

Discussion

We examined a set of articles drawn from the peer-reviewed literature on clinical genomics to see how CAS features could be leveraged in implementation efforts. We identified complexity features in all the papers we examined. Learning, sensemaking and adaptation were evident as teams observed results of their practice, reflected on their collective experience, and sought a better way forward. Anderson and colleagues[14] found their study challenged the logic behind their consenting process, as parents of their paediatric patients answered contrary to the expectations of clinicians and the policy guidelines of their peak professional body. Their reflection on the results led to sensemaking around a new concept they called "inflicted ought" to represent the burden of parents trying to do the best for their children yet at the cost of not doing the best for themselves. Another example of sensemaking was the refinement of the widely accepted concept of "clinical utility" by Nguyen and colleagues[15] to not be just a dimension of medical usefulness towards diagnosis and treatment but to include psychosocial components for both consumers and the health professionals involved in the genomic testing.

Interdependencies described were mostly around the need for collaboration between various disciplines (notably clinicians and laboratory scientists, laboratory scientists across different sites, and hospital-based clinicians, laboratory staff and researchers[4, 16-20]) to ensure robust and accurate genomic test results. The dependencies between the disciplines in genomic testing have been noted to be different from other areas of medical practice. The huge amount of data generated by the tests [49] (Thevenon and colleagues report a median of 4.8 gigabytes of result data per patient)[4, 21] require new processes to reach robust interpretation of results,[4, 20, 22] and often include review of recent literature, biostatistical analysis, consultation of databases from pooled variant data, and phenotypic input from clinical teams. The need to access and combine these highly specialised fields

of knowledge preclude a single professional group holding all the requisite expertise and assuming responsibility for the entire process,[20] showing the interdependencies of the different agents.

Another common interdependency was described in studies from the United States, where access to a genomic test was dependent on the patient receiving reimbursement from the insurer.[15, 23, 24] This was discussed as a barrier with significant consequences for patients unable to fund the test. Access to state-based support services for people struggling with a rare, debilitating disease was denied to patients without a formal diagnosis but the diagnosis could not be provided without insurance reimbursement for a genomic test.[15]

Self-organisation was frequently identified around the emergence of new roles and responsibilities in genomics[25] that in turn gave rise to novel or redefined collaborative relationships between health professionals.[4, 18, 20, 24] These emergent, novel ways of working are tightly linked to learning and sensemaking, as individuals and teams learn, make sense of, and respond to new situations encountered through the use of genomic testing. Moreover, recognition of emergent behaviours (including behaviours of patients[26] or parents of patients[14]) and self-organisation, acted as a catalyst to start projects that formalised new workflows, consent practices, or defined new communication protocols.[14, 26, 27]

It is possible that examples of self-organisation and emergent behaviours were underestimated. A key feature of CASs is dynamism. None of the included studies were longitudinal, although some studies compared before and after an intervention or compared a new process with business as usual. Even studies that explicitly use complexity theory do not always consider effects over time.[9] We speculate that examples of emergent behaviours or self-organisation would be more easily identified in longitudinal studies.

Uncertainty in genomic testing has been widely reported in the literature (for example, [28-31]) centering on unrealistic expectations of patients expecting a clear and unambiguous result, and the difficulties of interpreting variants of unknown specificity. It has been broadly discussed that genomic testing is often not a linear process driven by a single hypothesis, as in single gene testing. In single gene testing, a discrete hypothesis is tested, e.g., does this patient have cystic fibrosis? and a result is generated: yes, they do or no, they do not. Genomic testing on the other hand has been called “hypothesis-free”[32] and this explains some of its non-linear, unpredictable nature. For population-based studies the wealth of genetic data generated is mined to reveal patterns of disease-causing genes and variants, without the need for explicit predictions. While our study excluded these large exploratory studies and focussed on targeted clinical genomic testing, the uncertainty factor was still very much present. The majority of studies that gave details of genomic results reported unexpected diagnoses, variants of unknown significance, or secondary, incidental findings that could not have been expected from the clinical presentation of the patient. New research into disease causing genes and variants is constantly being added to pooled databases allowing stored genomic test results to be reanalysed at a later time. Again, a new and unexpected diagnosis could result. Further evidence of the uncertain and unpredictable outcomes of even targeted clinical genomics was the observation that software programs designed to facilitate robust analysis of results did not give consistent results.[16, 18, 20]

Leveraging of CAS features was demonstrated, or rather, could be deduced from the papers we analysed, in which features that were recognised by the researchers (authors) and then built on brought about improvements. Many projects reported learning and sensemaking from the feedback of patients, or their own experience of genomic testing and how they adapted and incorporated

those learnings into their practice (e.g., Dheensa and colleagues'[26] change of consenting processes to incorporate a discussion of ethical recontact procedures after the team reflected on patient feedback on the topic). Self-organisation and new interactions were seen frequently between disciplines involved in genomic testing as professionals found their own knowledge and skill sets incomplete to produce high quality results and sought the expertise of others (for example, the establishment of communication between clinical professionals and laboratory professionals described by Shashi et al).[24] Emergent behaviours were also used as the basis of a new, formalised way of working. Shyr and colleagues' study[17] on how different professions with different roles showed distinct preferences and patterns of working (i.e., emergent behaviours) around their use of genomic support software was the basis for future development of the software's usability features. Not all emergent behaviours were leveraged in this way. Garber and colleagues[16] described local emergent behaviours around laboratory conventions that were inconsistent and contributing to inaccurate results.

Interdependencies were described in the articles set in the United States between access to genomic testing and reimbursement by insurance companies. This interdependency was the focus of Lennertz and colleagues' project[23] using Agile methodology. This project leveraged sensemaking within self-organising teams to ensure optimal access through accurate and up to date information about entitlements for patients. Another interdependency that was recognised by some sites but not by others reported in the papers, was the link between comparative analysis of pooled genomic data and accurate genomic interpretations. This was achieved by sharing genomic test results across laboratories to benchmark interpretations and to build an adequate evidence base for rare diseases, for example in Thenenon and colleagues' study of French laboratories doing genomic analysis of paediatric patients with rare diseases.[4]

This paper has shown that across these studies, CAS features can and have been leveraged. While we acknowledge that a direct cause and effect is not able to be demonstrated,[9] it does suggest that better practice was built from the bottom up through the recognition of useful emergent behaviours and self-organisation, especially those arising from learning, reflection and subsequent sensemaking. Emergent behaviours that were not beneficial became targets for improvement. In addition, dependencies, once understood, were used to drive better organisation and efficiency. Unpredictable results and uncertainty were less likely to be leveraged but respected. The prerequisite for all these processes is a system-level perspective that does not shy away from contextual complexity.[2, 33]

Conclusion

All the articles reviewed were seen to have features of a CAS: interdependencies, learning, feedback, sensemaking and adaptation of practice, and emergent behaviours, uncertainty and self-organisation. Moreover, we were able to identify particular CAS features that were amenable to leverage to improve the quality and accuracy of testing. The recognition of emergent behaviours and self-organised teams, often arising from an earlier phase of learning and sensemaking could be built on to improve and formalise practice. Recognition of interdependencies led to research projects that optimised these interactions to drive beneficial outcomes. These studies suggest that leveraging the features of CASs is a viable strategy for improving the implementation of genomics.

Table 1: Critical review of articles showing examples of CAS features.

Reference	Focus of study	Do they describe sensemaking, learning, adapting?	Do they describe interdependencies, feedback loops and interconnections?	Do they describe self-organisation or emergence?	Do they describe non-linear, unpredictable processes or uncertainty?
Anderson 2016[14]	Consent process and return of clinically significant adult-onset incidental findings in a paediatric patient setting.	Unexpected responses by some parents in regard to disclosure of their own and their child's incidental findings led to staff reviewing the consent process and considering how to adapt it.	Parents and children's genomes are interconnected: clinically relevant incidental findings are as relevant to the parents and other family members as to the child (patient). Choices of parents are dependent on information given (or omitted) during the consent process.	Results led clinic staff to change their practice to meet local need, rather than only following top-down guidance of the peak body	Single gene testing is a linear process: test for gene x and results state if it is present or not. Genome testing is not linear as results may: be uncertain, may include incidental findings with their own implications, and may change in the light of new research and give a new / different diagnosis.
Dheensa 2017[26]	Issues around practical, appropriate and ethically sound recontact of patients when new research becomes available that is relevant to past tests.	Clinician-researchers learnt that there were no clear answers to the best way to recontact patients on the basis of new 'significant' information. They adapted practice by building recontacting issues into the consenting process.	Accessible past medical information and accessible new research are interconnected as the basis of appropriate recontact. 'Joint venture' model sets up an interdependency between the patient seeking an update and the health professional	The Clinic's health professionals are changing their practice in which the consent process and return of test results includes a discussion of recontact.	Other non-linear outcomes recognised: that even if patients are recontacted successfully about a clinically actionable finding, the patient could still choose to not act on it, negating the benefit envisioned. Unpredictable outcomes/unintended

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			providing expert review and advice.		consequences may come from putting responsibility for recontact onto patients, e.g., inequities based on the patient's ability to act.
Garber 2016[16]	Analysis and recommendations of variant discrepancies across labs with different processes	Amendments to the interpretation of variants were made as more information on them accumulated and were collated	Accurate interpretation of the significance of variants is dependent on multiple independent sources of information. Researchers are calling for more connections between labs to share data, and benchmark processes.	Locally-specific emergent behaviours were described within different laboratories (e.g., conventions around allele-frequency cut-offs).	Example given of unpredictable processes: a variant classified as benign in one data system and pathogenic in another – illustrating the need to review variant data from a range of sources.
Lennertz 2016[23]	Development of an 'Agile' system around assessing appropriateness and funding of genomic tests in a non-research, insurance-based context	Stories were developed (sensemaking) by groups to clarify tasks, expectations, responsibilities, and to refine practice.	Access to genomic testing and is dependent on reimbursement from insurers. Efficient administration of this is dependent on teams with clear understanding of insurers' rules and infrastructure for revenue management.	Agile methodology built on self-organising groups to define practice yet link them.	Non-linear process around the described work in that rules of insurers changed during the pilot requiring additional work to include more complicated requirements for reimbursement.
Nguyen, 2015[15]	Perspectives of physicians around	Health professionals understood the utility of	Access to support services are dependent	Behaviours around seeking funding for	Applying for funding was an unpredictable

Reference	Focus of study	Do they describe sensemaking, learning, adapting?	Do they describe interdependencies, feedback loops and interconnections?	Do they describe self-organisation or emergence?	Do they describe non-linear, unpredictable processes or uncertainty?
	appropriate, accessible, practical and acceptable use of exome sequencing in order to develop a broader conceptualisation of "clinical utility."	exome testing by considering psychological benefits and considerations around the wellbeing of the family, not just on whether a change of treatment resulted.	on a confirmed diagnosis, where the diagnosis defines the needs of the patient. However, access to diagnostic testing is dependent on other criteria meaning some patients are denied a test, a diagnosis and access to services.	exome testing have emerged to include a cost (time) to benefit calculation in response to experience: application forms are time consuming to complete and are often rejected.	process. Examples of physicians half filling out application forms then not proceeding as outcome was too uncertain.
Otten 2015[34]	Assessment of psychological benefits of group versus individual genetic counselling, and health professional satisfaction with the process.	Health professionals learnt from and planned to adapt the sessions, tailoring them to their participants in response to observed time issues and limited interaction.	The extent of participants' interactions were dependent on the number of sessions they shared together. As the pilot only had one session, interactions were limited.	Group genetic counselling being trialled here emerged from the problem of insufficient skilled workforce to handle one-on-one counselling.	The intervention had an unexpected benefit of increasing access for regional patients and education for regional health professionals. An unexpected drawback to group sessions was that it took more, not less time in preparation and follow-up.
Shashi 2016[24]	Developing a framework to categorise exome sequencing results by considering both laboratory and clinical information	By looking at retrospective cases and linking lab results with the clinical response to results, health professionals built a framework to provide a	Exome testing was dependent on patients having insurance coverage. Health professionals' ongoing use of exome	New communication paths were formalised between lab and clinic to report on phenotype and any new clinical presentations.	Analysis is not a linear process leading to a final result as it may change in the light of new research. This is in contrast to other tests

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	to enable reproducible and uniform communication of results to patients.	standard format and wording for results reports.	testing was dependent on their experience of being able /not able to understand implications of the result.		where a test result is final.
Shyr 2016[17]	Analysis of how different health professionals use exome or genome sequencing software tools and interfaces with a view to streamlining collaborative practice.	Software tools for exome sequencing are used by different professions undertaking different roles in interpreting results. By understanding different professions' needs, roles and preferences, software designers can develop future programs to support their shared work.	Multidisciplinary teams need to work together to accurately interpret results. They are dependent on other members of the team to perform their roles, and to share information, here within the shared software tool.	The way the tools were used showed emergent behaviour between professions: different parts were ignored or focussed on depending on the viewer's professional role.	Due to the multidisciplinary team approach to genomics, it was assumed that a single software tool would be most useful. However, since each group use the tool in a very different way, they suggest no single software program will meet all needs but may actually set up barriers for some.
Sperber, 2017[35]	Challenges and recommendations from a range of health professionals across different sites implementing clinical genomics.	Sites adjusted their interventions in response to what they learnt in preliminary planning stages. For example, one site presumed education on warfarin pharmacogenomics was only needed in	Education programs recognised the Interdependencies between clinical knowledge and knowledge of the electronic platforms being used.	Each site in the study had created its own clinical decision support rules, implying differing interpretation of needs and goals.	Some rules were not predictable. All sites but one routine had genomic testing for appropriate prescribing of clopidogrel. The other site acknowledged the utility of testing but unexpectedly did not

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		cardiology clinics but revised it to be system wide when understood multiple morbidities meant patients with cardiac issues could be treated anywhere.			allow testing outside clinical trials.
Taylor 2015[18]	Challenges and recommendations from a range of health professionals implementing clinical genomics.	False positive and false negative results were possible through use of isolated routine procedures, without seeking additional evidence. By using a two stage procedure they were able to improve accuracy.	Robust results are dependent on input from both labs and clinical teams.	Emergent collaboration between lab scientists and clinicians to achieve robust interpretations of results.	Comparison of different software systems that purported to do the same thing unexpectedly revealed that results achieved were markedly different.
Thevenon 2016[4]	Utility and application of exome sequencing for children with neurodevelopmental disorders.	Recognition that 6/14 diagnosed disorders had only been described since 2012 increased the perceived value of exome sequencing as it allows reanalysis as new research reveals more disease causing variants.	Accurate test interpretation is dependent on close collaboration between clinicians, geneticists, lab scientists and bioinformaticians.	Emergent collaboration of scientists and clinicians working towards accurate test interpretations.	While research is revealing more disease-causing variants thus increasing the likelihood of a diagnosis, it is also increasing the total number of uncertain variants and thus the likelihood of an uncertain result.
Uzilov 2016[27]	Utility and application of exome	Useful as more comprehensive testing	Better patient outcomes are dependent on	New workflow was developed by the	Study processes were not linear or predictable

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	sequencing within cancer care.	is, it was recognised that testing was time consuming and the high costs may not be reimbursed by insurers. This understanding is driving recommendations for a more focused, staggered approach to testing once research funding is no longer available.	reducing the long turnaround times for test results.	multidisciplinary team building on emergent behaviours (more comprehensive reporting) and self-organisation (how they were already working together collaboratively).	at times: some patients enrolled in the study died before their data could be analysed; some genomic testing could not be done because there was poor quality/insufficient samples.
Vissers, 2017[19]	Comparison of diagnostic processes for children with neurological disorders: exome sequencing versus standard diagnostic work up.	Review of results enabled clinicians to learn which cases were a cost effective use of exome sequencing, and those that were not.	Recognition of the interdependence of diagnosis and research: research is identifying more significant variants leading clinicians to believe that patients without a conclusive diagnosis will have it revised soon.	The health professionals involved were adjusting their post-test counselling and consent processes in response to interviews with parents of their patients.	An unpredicted result was that exome testing, although seen as the more comprehensive test, did not detect three disease causing mutations that were only picked up in the routine testing.
Vrijenhoek, 2015[20]	Assessment of different exome and genome diagnostic processes across eight clinical genetic clinics.	Clinics had learnt to "close the gap" to address suspected incomplete processing by running supplementary Sanger	Increasing interdependence of clinical teams, medical/lab scientists and research	The eight sites obtained largely consistent diagnoses prior to holding workshops that compared protocols and discussed how to	Unpredictable outcome described: data analysis packages purporting to do the same job did not give uniform results.

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		testing to obtain a more accurate result. Health professionals' understanding of clinical data from medical records had changed; from being a source of information to help choose which individual genes to test, to being a filter to assist in interpretation of variants.	departments to reach accurate diagnoses.	standardise processes, suggesting successful self-organisation.	

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