A model for mass personalization in cardiology: standard outcomes-based systems that can deliver personalized care

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ABSTRACT

Background

Even though there is excitement in the current healthcare environment on the potential of personalized medicine to utilize individuals' genomic data to improve patient outcomes and improve resource utilization, personalized medicine has not seen widespread adoption.

Main body

We explore how we can use the well-established principles of outcome-based healthcare system designed by the Value-Based Healthcare Programme at the University of Oxford to deliver better patient and population-level outcomes, encourage shared decision making, optimize resource utilization and to also deliver personalized care. This approach has been used to improve service delivery, improve outcomes and, importantly, drive culture change in England for a variety of different conditions since 2011. The approach, as applied to long QT Syndrome (LQTS), yielded two outcomes-based system specifications: one which outlines how to improve outcomes for patients with known LQTS; and a second which leverages genomic testing to identify people with unknown LQTS.

Conclusion

The simple approach outlined in this manuscript along with the context-independent and service agnostic systems presented have the potential to help deliver personalized care for cardiovascular diseases in a standard way.

BACKGROUND

There is much attention and excitement in the current healthcare environment on the potential of personalized medicine to utilize individuals' genomic data to improve patient outcomes and resource utilization. Despite tremendous promise, personalized medicine has not seen widespread adoption because of difficulties in achieving a balance between providing personalized care at a population level and delivering standardized care.

In this manuscript, we explore how we can use the well-established principles of outcomes-based healthcare system design developed by the Value-based Healthcare Programme at the University of Oxford[1,2] to deliver better patient and population-level outcomes, encourage shared decision making, optimize resource utilization, and to also deliver personalized care - i.e. mass personalization.

As a proof of concept, we apply this approach to long QT Syndrome (LQTS) and present outcomes-based systems which can be used for the effective reduction of risk of cardiac events (syncope, aborted cardiac arrest, or sudden cardiac death) in people with LQTS and their first-degree relatives.

MAIN TEXT

Designing outcomes-based systems

We used the 10 step model created by the Value-Based Healthcare Programme at the University of Oxford, which has been validated for several clinical conditions in England.[1] The model aims to maximize value and equity by focusing on populations defined by a common condition or characteristic through using a system approach.[2] According to this model, designing an ideal outcome-driven population-based system of care that delivers value to patients and populations requires 10 steps as illustrated in **Figure 1**.

Because of the focus on outcomes, the system design is flexible and it can be changed and adapted when new guidelines and best practices are revealed and also when innovative diagnostics and treatments are introduced. It takes a dedicated core group to take the initiative and start elaborating the subsequent steps. The scope of the system of care might be a symptom, a subgroup of population or condition as in this case. It is also essential to define the population to be served precisely, not only by naming it but also by specifying the practice and/or local authority. Although the aim of our system as applied to LQTS is set to reduce the risk of cardiac events in LQTS, it is important

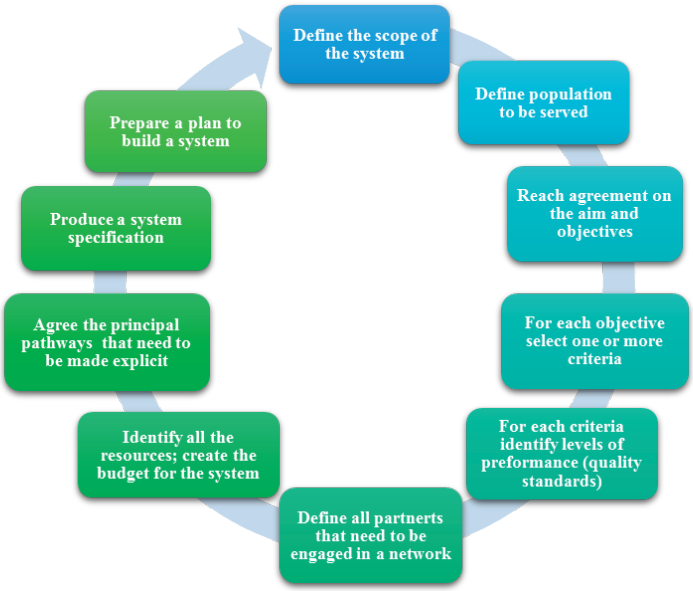

Figure 1. Steps required to design an outcome-driven population-based system of care according to the Value-Based Healthcare Programme at the University of Oxford.

to complement and supplement this aim with a set of objectives and one or more appropriate criteria to measure progress towards the objectives. The specific objectives and criteria for the LQTS system were defined based on expert consensus statement on the diagnosis and management of patients with LQTS and the Value-Based Healthcare Programme methodology.[2-4]

Long QT Syndrome

The value of screening for heritable cardiovascular diseases has been acknowledged by public health officials.[5] LQTS is an inherited heart rhythm disorder characterized by a prolonged ventricular repolarization (prolonged heart rate-corrected QT interval (QTc interval)) and T-wave abnormalities on the resting electrocardiogram (ECG), most commonly associated with specific ventricular tachyarrhythmia named torsade de pointes (TdP) which can cause syncope, aborted cardiac arrest and sudden cardiac death.[6-10] Occurring in approximately 1 individual in 2,500 worldwide,[11] LQTS is considered to be responsible for as many as 2,000-3,000 sudden deaths in children and young adults in the United States each year and 10-year mortality in untreated symptomatic cases is ~50%.[3,7,12]

The diagnosis of LQTS is either made when several ECGs with a clearly prolonged QTc interval are observed in the absence of acquired QTc interval prolonging factors, or

by use of a scoring system of clinical and ECG parameters.[3] Genetic testing is useful to make or exclude the diagnosis in borderline cases. In addition, genetic testing allows classification into LQTS subtypes by identifying the mutations in the genes coding for the ion channel subunits or the associated proteins.[4] At least 15 different genes are implicated in the development of 15 different LQTS subtypes (LQT1, LQT2, LQT3, and up to LQT15). The most common subtypes are due to mutations in three genes coding for pore-forming subunits of two potassium channels (*KCNQ1* and *KCNH2*) and a sodium channel (*SCN5a*) giving rise to LQT1, LQT2, and LQT3, respectively.[13]

The timely and accurate evaluation of the LQTS genotype has diagnostic, prognostic and therapeutic value, and thus an increased potential within clinical decision making.[14] In 2011, the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) developed an expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies.[3] The document provides a detailed analysis of the diagnostic, prognostic, and therapeutic impact of genetic test results for LQTS. First, the consensus statement recognizes its diagnostic value and recommends genetic testing for any index case in which LQTS is suspected by a cardiologist based on a patient's clinical history, family history, QTc interval, T-wave morphology and/or response to either cycle/treadmill or catecholamine stress testing. In addition, when a putative causative mutation is identified in clinically affected index cases, mutation-specific genetic testing of all first-degree relatives is recommended, even in the absence of a clinical and electrocardiographic phenotype.[3] Second, since numerous genotype-phenotype relationships pertain to the most frequent (i.e., LQT1, LQT2, and LQT3) subtypes, the LQTS genetic tests join traditional risk factors (i.e., gender, age, QTc interval at rest, syncope) as independent prognostic risk factors.[3] Third, LQTS genetic tests can influence clinical treatment decisions and it is recommended to incorporate genotype and mutation data with all other non-genetic risk factors in assessing the patient's risk and personalizing the patient's treatment plan.[3]

Genetic testing for the three most common LQTS subtypes in symptomatic index cases appears to be a cost-effective option as compared with no testing,[15] but further economic evaluations are needed to evaluate the value for money of testing asymptomatic first-degree relatives of a patient with established LQTS.[16]

Despite the fact that timely and accurate testing for the LQTS genotype has high positive predictive value and seems to be cost-effective, in many countries it is not used regularly in practice because of a lack of knowledge and service-level barriers to implementation. Furthermore, due to different standards, opinions and possibilities, it is not certain which intervention is optimal for every LQTS subtype, for example, different opinions

exist among experts on the treatment of LQTS3 (beta-blockers, flecainide, mexiletine, ranolazine).[17] To begin to tackle these issues, and improve transparency of choices and outcomes within and across services, we designed two outcomes-based systems: one for management of patients with identified LQTS; and the other to identify patients with LQTS who have not yet been identified. Our hope is that these systems will give a context-independent and service agnostic template for healthcare services to improve and personalize care for patients with LQTS and identify unmet need in their population.

Outcomes-based system for patients with known LQTS

The first system focuses on people with known LQTS and aims to reduce the risk of cardiac events in these patients. The population to be served should be defined by all the practices in the region. The objectives of the service, as well as the criteria used to measure progress towards the objectives, are listed in **Table 1**.

Table 1. Criteria defined to measure progress of each objective in the system aiming to reduce risk of cardiac events in patients diagnosed with LQTS

Objective	Criteria
To treat people with LQTS safely and effectively	- % of asymptomatic patients stratified by LQTS-subtype with a QTc-interval ≥ 470 ms who are on beta-blocker; - % of symptomatic patients stratified by LQTS-subtype who are on beta-blocker therapy; - % of patients in whom avoidance of QT-prolonging drugs is recommended; - % of patients who stopped beta-blocker therapy; - % of patients stratified by LQTS-subtype who had a cardiac event; - % of patients stratified by LQTS-subtype who are survivors of an aborted cardiac arrest in whom an implantable cardioverter-defibrillator (ICD) is implanted; - % of patients stratified by LQTS-subtype with ICD who received at least one inappropriate (not needed) shock; - Number of inappropriate shock/ICD complications; - % of patients with left cardiac sympathetic denervation who had a cardiac event; - % of genotype-positive phenotype-negative LQTS patients who are advised against participating in competitive sports;
To accurately assess the risk of cardiac events in patients with LQTS.	- Number of people known to have LQTS; - % of people diagnosed with LTQS who had age-stratified risk assessment by year-end using constellation of electrocardiographic, clinical, and genetic factors; - % of patients with LQTS who never had a risk assessment; - % of people with LQTS who had a risk assessment in the first year of treatment and who are in the second or subsequent year who have a review during the course of the year using age-stratified risk assessment based upon constellation of electrocardiographic, clinical, and genetic factors;

Table 1. Criteria defined to measure progress of each objective in the system aiming to reduce risk of cardiac events in patients diagnosed with LQTS (*continued*)

Objective	Criteria
To ensure patients with LQTS make informed decisions that take their values into account.	- % of patients who were explicitly told that a choice for treatment is to be made and that the patient's opinion is important; - % of patients whom the options and pros and cons of each relevant option were discussed with using the available information aids (graphics, decision aids, decision grids); - % of patients whose patients preferences and underlying values were discussed; - % of patients whose decisional role preference was discussed as well as possible follow-up; - % of patients who feel they were adequately involved in decision making; - % of patients in whom beta-blockers are indicated who know the main pros and cons of beta-blocker therapy; - % of patients in whom ICD is indicated who know the main pros and cons of ICD implant;
To make the best use of resources.	- Mean cost of beta-blocker therapy; - Mean cost of ICD implantations; - Mean cost of molecular genetic testing; - Estimated cost of avoidable cardiac events; - Service cost/patient;
To promote and support research.	- Capture awareness of research undertaken; - Proportion of units with a defined person having a lead role to promote research and number of research publications; - % of staff undertaking research related course at university;
To train the professionals who support patients with LQTS.	- Structured education, consultation skills, and attitudes; - % of patients that are seen by an integrated, multidisciplinary team and expertise assessing them (cardiologist, nurses, mental health professionals, pharmacists); - % of staff trained in ECG;
To produce an annual report for the population served and to support quality improvement.	

Outcomes-based system for patients with LQTS who have not been identified

The second system focuses on family members of patients with LQTS in whom LQTS has not been recognized. The aim is to reduce the risk of cardiac events in these unidentified patients. The population to be served should be defined by all the practices in the region and the objectives and criteria of the service are listed in **Table 2**.

Table 2. Criteria defined to measure progress of each objective in the system aiming to reduce risk of cardiac events in family members of people with LQTS in whom LQTS has not been recognized yet

Objective	Criteria
To diagnose LQTS accurately in asymptomatic family members of LQTS patients	- Number of people with known LQTS; - Number of patients with known LQTS and confirmed genetic mutation; - Number of first degree relatives (parents, siblings and/or children) of LQTS patient that were informed and choosing to have or not to have molecular genetic testing (in a case mutation is known); - Number of first degree relatives (parents, siblings and/or children) of LQTS patient in whom molecular genetic testing confirmed genetic mutation and choosing to visit a cardiologist; - Number of first degree relatives (parents, siblings and/or children) of LQTS patient that were informed and choosing to have a cardiological examination (if no mutation is known); - % of first degree relatives (parents, siblings and/or children) of LQTS patient with prolonged QTc interval on ECG;
To treat an asymptomatic family member of LQTS patients safely and effectively.	- % of first degree relatives (parents, siblings and/or children) of patients with LQTS stratified on the basis of the LQTS-subtype with prolonged QTc-interval on ECG (≥ 470 ms) who are on beta-blocker therapy; - Number of first-degree relatives (parents, siblings and/or children) of patients with LQTS with failure to tolerate beta-blocker therapy; - % of first degree relatives of patients with LQTS stratified by age (children/adults) with normal QTc interval on ECG and positive genetic diagnosis who are on beta-blocker therapy (all and stratified by LQTS-subtype);
To accurately assess the risk of cardiac events in an asymptomatic family member of LQTS patients.	- % of first degree relatives of patients with LQTS who had age-stratified risk assessment by year-end using constellation of electrocardiographic, clinical, and genetic factors; - % of first degree relatives of patients with LQTS who had a risk assessment in the first year and who are in the second or subsequent year who have a review during the course of the year using age-stratified risk assessment based upon constellation of electrocardiographic, clinical, and genetic factors;
To ensure that asymptomatic family members of patients with LQTS make informed decisions that take their values into account.	- % of first degree relatives of patients with LQTS who were told their disease risk; - % of first degree relatives of patients with LQTS who participated in the decision to either undergo a particular form of screening and genetic testing or not; - % of first degree relatives of patients with LQTS who were explicitly told that a choice for treatment is to be made and that their opinion is important; - % of first degree relatives of patients with LQTS whom the options and pros and cons of each relevant treatment option were discussed with; - % of first degree relatives of patients with LQTS whose patients' preferences and underlying values were discussed; - % of first degree relatives of patients with LQTS whose decisional role preference was discussed as well as possible follow-up; - % of first degree relatives of patients with LQTS who feel they were adequately involved in decision making; - % of first degree relatives of patients with LQTS who know the main benefit and main risk of beta-blocker therapy;
To make the best use of resources.	- Mean cost of beta-adrenergic blockade therapy; - Mean cost of molecular genetic testing; - Service cost/patient;

Table 2. Criteria defined to measure progress of each objective in the system aiming to reduce risk of cardiac events in family members of people with LQTS in whom LQTS has not been recognized yet (*continued*)

Objective	Criteria
To promote and support research.	- Capture awareness of research undertaken; - Proportion of units with a defined person having a lead role to promote research; - % of staff undertaking research related courses at university;
To train the professionals	- Structured education, consultation skills, and attitudes; - Integrated, multidisciplinary team, and expertise (cardiologist, nurses, mental health professionals, pharmacists);
To produce an annual report for the population served and to support quality improvement.	

CONCLUSIONS

A major promise of the information deriving from 'omics' research is the transformation of healthcare and clinical decision-making through effective prevention programs, earlier diseases diagnosis and prognosis, and personalized treatments.[18] In this manuscript, we present an approach that can be used to deliver personalized care in a standardized way for LQTS, a condition for which genetic testing can provide new opportunities for patients' management, as stated by the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA).[3]

Our work yielded two outcomes-based systems designed to reduce the risk of cardiac events in people with known LQTS and those who have LQTS but have not been identified. The systems are specifically designed to focus on the patient outcomes, which means that the systems are service agnostic, context-independent and applicable in a variety of healthcare organizations irrespective of resource constraints. Healthcare services can use these systems as a starting point to design their LQTS-focused healthcare services to focus more on patient outcomes and personalized care, while also tracking resource utilization for their services.

A key aspect of the systems is the requirement to produce an annual report that records data on outcomes delivered as well as resources used - thus giving an indication of the value (outcomes/resources used) of the service. We acknowledge that initially, the data will not be perfect - it may not be complete and the quality may not be great. Furthermore, even when there is agreement with the objectives and criteria, getting everyone in the system to work in a coordinated way and break down artificial silos may also be difficult. However, it is important to start shifting the culture and working practice of

one's healthcare service to begin to think in a different way about how their service is designed and delivered and, most importantly, what it is accountable for. The data from annual reports can be used to:

- Determine how your service is evolving over time
- Identify gaps and/or areas where your service is not doing well (e.g. underuse/ underdiagnosis)
- Identify wasted resources in your service
- Determine how your service compares to other services serving similar demographics
- Improve transparency of choices and outcomes

The ultimate ambition in presenting this work is to create a learning and sharing network to identify new best practices as well as innovations, service level as well as technical, which can be used to deliver better outcomes, and optimize resource utilization, to patients and populations with LQTS globally.

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