Patient and Public Involvement in the adoption of stratified medicine

A summary report on a focused workshop held by Pharmacogenetics and Stratified Medicine Network, London, November 2015

Introduction

Patients and the general public must be supported so as to fully understand the shift away from the traditional "signs and symptoms of disease based medicine" and appreciate the benefits of using genetics, and other bespoke diagnostic tests, to identify subcategories of disease on which clinicians may base their diagnosis and prescribe the most appropriate medical treatment. This more "tailored approach of prescribing" has been described as either stratified, personalised, precision or P4 medicine and benefits the patient as they receive the most appropriate drug at the start of their treatment, at the correct dose and in the right combination with their other medications. Stratified medicine simply means that patients are put into categories according to the subtype of their disease and then given the medical treatment most likely to have a positive therapeutic effect.

This report summarises the findings of a focused workshop where a group of senior representatives from academic and clinical research organisations, industry and regulators, met with representatives from patient groups to discuss, and address, three main issues around the adoption of stratified medicine into the clinic, namely:-

- Public and Patient Involvement in stratified medicine
- Ethical and legal issues around using electronic health data for stratified medicine
- How to make stratified medicine a reality in the UK

Speakers' presentations from the workshop may be found online at http://www.uk-pgx-stratmed.co.uk/index.php/workshops.html

Patient & Public Involvement in Stratified medicine

Public Patient Involvement (PPI) is the active partnership between the public, patients and clinical researchers, in the whole disease research and treatment process and is critical to increase both public acceptance of stratified medicine and patient participation. It is recognised that patient engagement with stratified medicine is crucial to obtain the samples and data required for researchers to identify the subcategories of disease; and for industry to go on and develop diagnostic tests and much needed new drugs to treat patients. In areas where there is an awareness and understanding of stratified medicine, patients and the public are enthusiastic towards its

adoption. However, patient expectations must be carefully managed to ensure they are not over burdened with information nor do they have unrealistic expectations of their treatments.

Patients are willing to be involved with formulating ideas for research, and the design of both research protocols and clinical trials to bring about improvements in clinical care. Initiatives such as Citizen Science, Consent for Consent and NHS OK to ask, have supported public engagement with research and increased patient recruitment to clinical trials. This input from patients brings many benefits to researches; for example, discussions with patients prior to initiating research projects help the researcher focus on what questions are important to patients. Patients advising on the design of clinical trials ensure that the trial is easy to follow increasing patient compliance and ultimately improving the quality of the trial. It should be noted it is often essential to have patient involvement to gain ethical permission for conducting the clinical trial and patients sitting on medical ethics committees contribute to making consent forms and information sheets more relevant and understandable to the lay person.

Stratified medicine role in preventative medicine

A stratified medicine approach not only improves targeted drug delivery but it also plays an important role in preventative medicine. Previously disease risk stratification was limited to large general categories related to the broad groups of age, sex, or particular identifiable lifestyles such as smoking, lack of exercise, poor diet etc. Analysis of patient data acquired from new technologies, such as genetic sequencing, allows the stratification of the population into groups of those at high, medium or low risk of disease and then offers interventions to help prevent the onset of disease. These interventions may involve clinical treatments or simply suggest lifestyle changes to prevent onset of disease. For example, changes in diet and increased exercise may prevent Type II diabetes.

Determining the disease risk stratification of individuals has the advantage of identifying, and then screening, only those patients at increased risk of diseases, thus reducing the number of routine tests carried out and so lowers overall screening costs. It has the added potential advantage of avoiding over-diagnosis by reducing un-necessary biopsy follow-up testing of false positive routine screening results and decreases the numbers of patients becoming the “worried well” when part of screening programmes. However, there are some concerns about the accuracy of patient data used to stratify patients, so specialist knowledge is required to correctly interpret the data to provide true, accurate risk models. The public have come to expect mass screening programmes so some may actually want to be part of a regular screening programme to feel protected from the risk of disease. There is a chance stratified screening programmes may miss some individuals and the question arises is it ethical to select a sub-population of patients to screen when there may only be a small difference in the increased level of risk they face in developing diseases such as breast or prostate cancer? Therefore, a stratified approach to preventative medicine must be carefully managed to take into account true risk factors and public expectations of screening programmes. The public must be provided with an understanding of their true risk factor of disease without being overburdened with complex genetic or diagnostic information to provide reassurance that stratified screening programmes are effective in preventing disease.

Use of genetic data in stratified medicine

Pharmacogenetics, the study of a patient's genetic data and their response to drug treatments, plays an important role in the adoption of stratified medicine. Patient data is a valuable commodity to researchers as it plays a vital role in identifying the molecular / genetic subtypes of disease and allows analysis of how each patient responds to a particular drug therapy during a clinical trial. Patient data is also essential for the pharma industry to identify the molecular targets against which to develop much needed new niche market drugs to treat each individual subtype of disease. Patients must be made aware of the value of their data and should be encouraged to fully understand how it is being used before they are asked to provide consent to the use of their data by researchers and commercial organisations. Patients are generally very altruistic and are willing to donate their samples and data, but must be given reassurance that the data is used ethically, stored securely and is making a difference to research. Patient representatives on ethics committees encourage a higher level of transparency of the use of data and so help gain public confidence and support for research.

The increase in commercially available genetic testing, potentially even including direct to consumer genetic testing, needs careful consideration and the public must be made aware of the need for data analysis by experts who are trained to determine the clinical relevance of any genetic mutations uncovered. Many asymptomatic heterozygotes or 'carriers' of a genetic mutation live normal healthy lives but may require appropriate genetic counselling to help them make informed choices about their health monitoring and impartial, accurate genetic risk information to support reproductive decisions. Genetic councillors must also be available to support patients when unsolicited findings reveal an unexpected potential for a disease, especially following genetic testing of minors.

Ethical and legal issues around using electronic health data for stratified medicine

Patient data is collected from multiple sources, including during routine healthcare visits, as part of undergoing diagnostic testing for disease, or when a patient has enrolled in a research clinical trial. Data is collected in many different formats and may include high dimensional datasets, such as genomic and imaging diagnostic data or clinical data from small research studies, and is stored as patient Electronic Health Records (EHRs). Currently the data is collated in different formats which are often not always compatible and there is a lack of adequate infrastructures for data transfer between different clinical specialties and healthcare providers. Furthermore, the consistency and specificity in terminologies used and phenotypic coding information recorded is often not in a uniform format which makes some of the data inaccessible for research purposes. Using more structured EHRs would greatly increase their utility, so currently the key challenge is to change practice and collate all EHRs in a compatible format, and encourage medical professionals to use a standard format when collecting the data, especially phenotypic information.

Analysis of this 'big data' is challenging as there are constraints within the analytical methods available and currently there are not enough bioinformaticians trained to study all the existing clinical data and retrieve the emerging patterns. In addition algorithms to mine the data need to be scalable to a level where they are suitable for managing the large amount of diverse data collated.

Increased use of automation in the format of machine learning would help to capture content from 'data rich' text. Developing a "uniform natural language" would enable relevant phenotypic descriptors to be more easily detected and collated from the existing data. Furthermore, greater use of patient-held records, where patients bring their records on hand held electronic devices to each healthcare appointment, would reduce the extent to which data remains in siloes that are relatively inaccessible between clinical specialties and so facilitate better data integration. Finally, more closely aligning reimbursement mechanisms with real-world utility could improve the design and effectiveness of clinical trials and further the adoption of stratified medicine within the clinic.

Patient consent

Obtaining patient consent to use the biological samples collected during their treatment to determine the molecular basis of disease and using the accompanying EHRs to group patients for clinical trials of new drugs is an important issue for moving stratified medicine forward. Patients are often supportive of the use of their samples but have concerns over the security of their data and their right to privacy. There are regulatory processes and legal limits in place defining how data may be accessed, shared and used by third parties, but the ethical concerns include the underlying philosophical issues around patient consent are not so well defined. Participants in a clinical trial may often have limited the breadth and scope of their consent resulting in restrictions on how data is shared for both clinical care and research. Poor communication and a lack of patients understanding of the need to provide a broader range of consent may further aggravate these restrictions.

Some patients do not want to know about their future health risks, or those of their family members. Generally, it has been considered not to be ethical to genetically test children for adult onset diseases as they would not have any input to the consent process for such tests. Such tests would not necessarily determine the severity of how a disease would progress and may overburden the patient with concerns about their future health. However, it has been suggested that there are justifications to genotype neonates, infants or young children for genetic variants associated with common cancer development as part of a personalised screening programme. In this case potential benefits, including improved-diagnosis, may outweigh potential harms of not preserving a young person's autonomy.

Who receives medication and when

The potential ethical issues relating to 'who receives stratified medicine and at what stage of their disease' should be considered in context of risk/benefit to the patient. It is important to manage patient's expectations so that they feel treatment is distributed fairly and that no healthcare inequalities are introduced through the introduction of stratified medicine. Low risk category patients must not feel as if they have been deprived of either a treatment or monitoring of their condition. Issues also arise around the question of patients taking personal responsibility for a change in lifestyle to alleviate their condition rather than automatically receiving a clinical intervention or treatment. Patients want to have autonomy and to make a contribution to the decision alongside clinicians about their treatment at different stages of their disease progression rather than the treating physician dictating their treatment. Providing patients with a better understanding of their treatment, and an input into the choice of treatment they receive, has the

advantage of making patients more engaged with their healthcare and ultimately more compliant with their treatment.

How to make stratified medicine a reality in the UK

To bring stratified medicine into mainstream healthcare there is a need to significantly widen public understanding of the potential benefits of stratified medicine by reaching out to, and engaging extensively with, more patient groups, disease research charities, regulators, healthcare providers and industry. Currently it is generally only the more educated patient that has an understanding of stratified medicine so it is important that all age groups, and those from divergent ethnic backgrounds, are reached and informed about the benefits of stratified medicine to avoid inequalities in delivering healthcare. The message must be portrayed in a variety of formats that are aimed at each individual group and in a language suited to the target audience. Lessons on how to deliver effective public engagement can be learnt from examples of how charitable organisations reach out into the community with activities such as local educational or fun day events to gain public support. Patients who have an understanding, or have had experience of receiving a stratified treatment, becoming ambassadors would be another valuable resource to support developing effect PPI.

Education and training

For stratified medicine to become commonplace there is a need for all stakeholders (including healthcare providers, patients, researchers, regulators and industry) to have broader understanding of the issues around delivering this new approach to patient care. The public may not always mirror the concerns of the medical profession so PPI that is truly patient led is essential to ensure that the science underpinning the discipline is aligned with the needs, understanding and expectations of society as a whole. Misrepresented or ineffective communication of the function and appropriate use of evolving technologies to patients may cause misunderstanding and alienation of patients if they feel they are not receiving the latest treatments. If full advantage is not taken of emerging technologies there is a risk of potentially increasing health inequalities rather than reducing them. Therefore an integrative approach is required to improve the quality and consistency of the message to both the public and healthcare professionals that technologies used to deliver stratified medicine are a positive change that will bring significant improvements to patient care across all medical disciplines.

High quality information presented in a comprehensive format tailored to the needs, specific backgrounds, and level of knowledge, is required to educate the public. This will require a significant co-ordinated outreach programme to engage with all groups of the public to ensure that the appropriate messages are conveyed and that the language is always suited to the audience, or there is a danger that sectors of the public and patients will be overlooked. However, a campaign to deliver education at a national level to the public would require access to a significant amount of new funding and support from both patient groups and medical charities.

Education, training and effective communication must also be built into the everyday work of doctors, nurses and other allied health professionals, such as pharmacists, dieticians etc.,

throughout all clinical specialties and at all levels from undergraduate to continuing professional development, or some healthcare professionals will not engage with the introduction of stratified medicine. This again will require substantial and sustained resources in order to lead and undertake strategic planning to put in place a broad framework to co-ordinate the development of training programmes to deliver education across the NHS, and for practitioners themselves to be encouraged to undertake the necessary training. Therefore, a wide range of organisations such as Health Education England, the General Medical Council, plus Royal Colleges and Deaneries, must be involved as well as Higher Education providers to educate healthcare professionals. Clinical champions already practising stratified medicine leading engagement will be required to encourage engagement at Trust and Clinical commissioning group levels. Initiatives such as the new Masters level courses in Genomics Medicine have been started in support of the 100,000 Genomes Project but there are concerns that this will not reach enough individuals and the course may not be sufficiently clinically orientated to have the required impact on medical practice. Open access to online peer-reviewed scholarly research and literature will support CPD and should be further developed and made available to all.

Understanding and tackling perceived "negatives"

Accurate perceptions of the benefits of stratified medicine, including improved understanding of disease biology and how this leads to the development of treatments with more certainty of positive outcomes for diseases are, at best, sporadic. Expectations are often unrealistic and predicated on poor reporting of the latest examples of stratified medicine in the popular media. If these concerns are not addressed in an appropriate and timely fashion, there are potential risks to improving public and patient engagement and acceptance of stratified medicine. Lessons may be learnt from how the use of genetically modified crops was introduced to the public. Due to negative press coverage and lack of education it has taken a long time for the public to understand the benefits of the genetic modification of crops and to trust the use of the technology. Therefore, PPI must deliver a balanced message, detailing both the expected positives and potential predictable negatives of stratified medicine to gain public support. Expert ethical and legal oversight may be required prior to introduce large scale implementation of stratified medicine in order to ensure that societal concerns are addressed, and dealt with appropriately, before changes occur to patient clinical pathways.

Having a properly resourced and actioned PPI support strategy in place from the outset will be invaluable in the event of any unintended consequences becoming apparent. If a patient and public-centred discussion about the potential benefits of stratified medicine has already occurred, leading to an overall positive view of the technology and its purpose, then the effects of any unforeseen negative event will likely be somewhat mitigated. Any negative publicity may then be dealt with effectively as soon as it occurs so it does not threaten to reduce participation or potentially the entire viability of stratified medicine within the national healthcare system.

Systems change

The implementation of stratified medicine will require significant changes in delivery of healthcare systems as it involves more than just a question of substituting one specific diagnostic or treatment for another. Entire clinical pathways will need to be reengineered to ensure that patients are managed appropriately at the individual level and receive the appropriate diagnostic tests to determine their treatments at the optimum time during their care. Furthermore, a whole new

infrastructure will be required to support both the structure and activities of these new healthcare systems. For example, methods to capture, store, share and release patient data will have to be developed similar to Clinical Practice Research Datalink already in operation.

It is also important that the range and quality of information provided in test results is standardised and reported in a "user friendly" format to improve quality and support the decision-making process for the referring physician, who is likely to have limited genomics expertise. For example, genetic test results should be presented to patients and their physicians in a way that clearly states the likely relevance (or even uncertainty) of any genetic variation found to the clinical question and how it may impact on the choice of treatment. There are some aspects of the way commercial test results are presented direct to consumers that might provide lessons on clear risk communication for other healthcare services.

At present the implementation of stratified medicine thrives in particular medical disciplines such as oncology and is not co-ordinated or well publicised in other areas. Ultimately there is a need for a more integrated framework across clinical and research activities for delivering stratified medicine which is focused on using high quality research to underpin improving the quality of care. For example, researchers gain access to the genomic data collected from 100,000 patients suffering with rare diseases through Genomics England Clinical Interpretation Partnerships will help diagnose these rare diseases and help determine how to best develop treatments for them.

Industry support for stratified medicine

Technological advances, particularly in genomics, have revealed that there are many different subcategories within each disease. Industry will play a vital role in changing from developing block buster drugs that are prescribed to all patients suffering with a disease with only limited efficacy; to developing new drugs targeted to treat each subtype of disease with a higher level of efficacy. However, both disease and drug response heterogeneity must first be established, along with the feasibility of developing a relevant diagnostic test to identify the subcategory of disease, for there to be an incentive for industry to develop such niche market drugs. Developing a specific biomarker, or diagnostic test, that distinguishes subcategories of disease and aligning a specific drug treatment to that category of patients will potentially result in significantly improving drug efficacy. Furthermore, using these tests to predict how a patient will react to a drug will increase drug safely by reducing the number of adverse drug reactions patients experience.

When developing a biomarker to aid clinical decisions on patient treatment a balance has to be made around the needs of patients as well as the other stakeholders involved; including those using the test for diagnosis, those funding the test/treatment and regulators who must licence the products. Physicians are less concerned about non-responders to a drug and want the test to be 90% accurate in detecting negative results as they do not want to exclude treating patients on the basis of a false negative result. Patients want a reliable early diagnosis of their condition so they are not left with the worry about how their condition is going to progress and affect their future health. Those funding the development and licensing the test want a degree of certainty that it will deliver a positive outcome in terms of the treatment increasing the quality of adjusted life years for the patient before they invest in the test. Finally, the accuracy and reliability of the biomarker must be validated clinically to provide both clinicians and patients with confidence in the test. There are issues to be resolved around how funding should be put in place for both the development of

diagnostic tests and end-use of the tests in the clinic. The tests are often developed by SMEs and academic spin-off companies and currently there is no re-imbursement scheme within the NHS to fund end-use of specific diagnostic tests for stratified medicine.

Summary

The report has highlighted some of the challenges facing gaining patient and public support for the widespread introduction of stratified medicine into the clinic. However, there are many examples of how using a stratified medicine approach has brought great improvements in patient care and the current advances at pace of emerging technologies will provide us with ever more opportunities to offer patients the most appropriate drug, at the start of their treatment, in the optimum dose and best combination with their other medications.