Discussion of “Combining Health Data Uses to Ignite Health System Learning”

S. Denaxas1,2; C. P. Friedman3; A. Geissbuhler4; H. Hemingway1,2; D. Kalra5; M. Kimura6; K. A. Kuhn7; H. A. Payne6; F. G. B. de Quiros8; J. C. Wyatt10,11

1Institute of Health Informatics, University College London, London, United Kingdom; 2Farr Institute of Health Informatics Research, London, United Kingdom; 3Department of Learning Health Sciences, University of Michigan, Ann Arbor, USA; 4Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland; 5The EuroRec Institute, Gent, Belgium; 6Hamamatsu University, School of Medicine, Department of Medical Informatics, Hamamatsu, Japan; 7Technische Universität München, Chair of Medical Informatics, Munich, Germany; 8University of Washington, Department of Medicine, UW Medicine IT Services, Seattle, USA; 9Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 10University of Leeds, Leeds Institutes of Health Sciences and Data Analytics, Leeds, United Kingdom; 11University of Southampton, Wessex Institute of Health, Southampton, United Kingdom (from 2016–01–01)

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Summary
This article is part of a For-Discussion-Section of Methods of Information in Medicine about the paper “Combining Health Data Uses to Ignite Health System Learning” written by John D. Ainsworth and Iain E. Buchan [1]. It is introduced by an editorial. This article contains the combined commentaries invited to independently comment on the paper of Ainsworth and Buchan. In subsequent issues the discussion can continue through letters to the editor. With these comments on the paper “Combining Health Data Uses to Ignite Health System Learning”, written by John D. Ainsworth and Iain E. Buchan [1], the journal seeks to stimulate a broad discussion on new ways for combining data sources for the reuse of health data in order to identify new opportunities for health system learning. An international group of experts has been invited by the editor of Methods to comment on this paper. Each of the invited commentaries forms one section of this paper.

Correspondence to:
See list of authors’ addresses at the end of the article

1. Comment by S. Denaxas and H. Hemingway

The manuscript of Ainsworth and Buchan [1] has much to commend it in stimulating and focussing debate based on a distillate of experience originally in the north west of England and more recently across the UK Farr Institute. Inevitably it raises many questions if we are to meet the challenges of ‘data based medicine’ in its broadest sense. While there are efforts to curate big data to knowledge (BD2K) with linked electronic health records (e.g. CALIBER [2, 3]) much of the knowledge to practice (K2P) efforts have been separate. Importantly Ainsworth and Buchan illustrate ways of integrating the so-called afferent and efferent arms, the brain and the spinal cord. Many questions of course remain and we would highlight the following.

1.1 Learning Health Systems at Small and Large Scale: Universal and Private

The UK National Health Service is a universal healthcare system, free at the point of use. To what extent does the conceptual framework described scale from the north west of England to the UK generally? Including larger number of patients, health care providers and datasets is likely to pose significant challenges, some of which would not have been previously encountered [4]. Furthermore, to what extent does the architecture proposed scale to private hospitals, whose ‘health system’ is competitive, and may have a very different view of public health.

1.2 Are Learning Health Systems Effective?

The extent to which health systems can be described as ‘learning’ and the richness of their use of data in clinical decision-making can in principle be measured and seen as technologies and complex interventions which can (and should) be subject to empirical evaluation. The authors provide a theoretical measure of evaluation, the Data-Action Latency (LDA) metric, defined as the time lag between actionable data being available and the action being executed. Such a specific metric is useful,
but the wider impact on the effectiveness of data-based healthcare processes demands scrutiny.

A range of observational (e.g. before and after, natural experiment, geographical comparison) and experimental (e.g. cluster randomised trial) designs are relevant: and the outcomes evaluated should be broad, including clinical, social outcomes (e.g. education, employment) and costs. These will require linkage of data sources located outside the Ark and inside other administrative strata such as government bodies and departments. Empirical evaluation should be a continuous process, with both metrics and outcomes constantly evaluated and recalibrated.

1.3 Linking Genome to Phenome

We are arguably entering the era of data-driven and data-intensive, personalized medicine, where electronic health records are considered the transformational force for measuring and improving the quality of clinical care and accelerating the pace of biomedical research. This has been exemplified by multiple strategic initiatives in the USA and the UK. The USD$ 215 million Precision Medicine Initiative [5] was announced by the US government and aims to create a research cohort of at least 1m adults with genomic and EHR data. In the UK, Genomics England, is aiming to sequence 100,000 whole genomes during routine clinical care and the UK Biobank [6], a population research cohort has recruited 500,000 middle-aged participants and offers a multitude of rich phenotypic data including national EHR linkages and MRI imaging data. Such initiatives should also be taken into consideration as个性化 care by definition will increasingly involve knowledge obtained from genetic data combined with phenotypic information in order to provide accurate diagnostic and therapeutic approaches to patients. Moreover, the domain of bioinformatics has taken great strides towards standardizing raw data and methods, both fields in which clinical research currently lacks [7]. Closer interaction with scientists from the field will provide insight on best practices, giving us the opportunity to re-use them.

1.4 EHR-driven Clinical Trials Pipelines

There is an urgent need for the articulation and integration of clinical trial pipelines at the point of care, fuelled by big data technologies [8]. The integration of digital recruitment, consent and randomization at the point of care would enable clinicians to aggregate and leverage retrospective patient data in the absence of trial data matching the profile of the encountered patient. Technologies such as the "green button" [9] could potentially allow clinicians to leverage aggregate patient data for decision-making and facilitate EHR-enabled randomization at the point of care in the absence of gold-standard evidence.

1.5 Streamlined Information Governance

The complex information governance restrictions associated with each external data custodian (e.g. the Health and Social Care Information Centre, the provider of national hospitalization EHR data in the UK) often translates to very long periods of time before clinical data are made available or make linkages between sources challenging. We argue that these issues are critical and have to be considered and addressed in parallel in order to reach an optimal solution which enables the exploitation of such data under a streamlined governance framework. A proportional governance model combined with streamlined ethical and governance requirements across key data stakeholders and public engagement would enable clinicians and researchers to spend less time obtaining the data and more time analysing it for answering clinically meaningful questions.

1.6 Conclusion

In conclusion, this article we hope will act as fuel, igniting the debates that will lead to the transformative changes the authors describe within the healthcare system. We do exercise a certain degree of caution however; the current challenges faced do not neatly fall into pre-defined categories but form a network of overlapping areas with complex relationships and dependencies. The optimal solution therefore will require multiple iterations to achieve, and along the same lines, would need to be constantly evaluated and recalibrated in order to retain its effectiveness.

2. Comment by C. P. Friedman

In my own recent thinking about the necessary attributes of a large scale, sustainable Learning Health System, I have come to identify four that seem most important: inclusiveness, trust, decentralization, and reciprocity. In this brief commentary, I will first describe each of these attributes and then describe, as a major strength of their paper, how Ainsworth and Buchan [1] bring all of these concepts to light.

Inclusiveness refers to the necessary presence and active participation of all health stakeholders within the national or sub-national scope of the system. Possible stakeholders include, but are not restricted to: provider organizations, payers insurers, patient groups, government and public health agencies, pharmaceutical and technical firms, as well as universities and research institutes. The LHS, in this sense, can be likened to an atomic nucleus, which goes unstable if it loses one constituent particle.

All of these stakeholders must then also trust the system. In this context, trust transcends the necessary respect for privacy of all participants who contribute data to the system and their ability to maintain the security of those data. Trust extends to a belief in the validity of both the knowledge that the LHS will provide, and the messages that stakeholders will receive, stemming from that knowledge.

Decentralization refers to governance of the system that is not strictly top-down or otherwise dominated by the any of the participating stakeholders. All stakeholders must share in making the important decisions about the system's ongoing function. Domination of the policy-making within the LHS by any one group or member of a particular group will – particularly in a competitive environment among some of these stakeholders – cause others to leave
the system and make it unstable. Although decentralization is also often taken to refer to distributed data stores and federated networks, many different technical configurations of an LHS can be successful as long as the governance is appropriately configured.

Reciprocity refers to the requirement that all stakeholders in a stable LHS must put something important into the system, and obtain something valuable in return. Not all stakeholders will contribute the same resources. For example, some will contribute data; others will contribute technological resources; and still others will contribute money. In return, these different stakeholders will be attracted to and find useful very different kinds of knowledge the system produces. In the end, a stable and successful LHS requires that the value to each stakeholder of what is received from the system exceeds the cost to them of what they contribute.

A major strength of Ainsworth and Buchan’s vision for the LHS is their success in addressing all four of these key ingredients, and offering models through which these requirements might be achieved. Their attention to these ingredients runs through their entire work, and each typically appears multiple times.

Their Figure 3 provides a clear illustration of the multi-stakeholder aspect of the LHS. Their fascinating concept of the “Ark” brings this into clear focus. After all, what entity more completely engaged all stakeholders more than Noah’s Ark? Of course, all metaphors have their limitations, and the extreme exclusivity of Noah’s Ark – one couple per species – could be seen as running counter to the spirit and core values of the LHS.

The concept of trust appears repeatedly in their essay. In Figure 2, which conveys their concept of the evidence pipeline, they specifically cite each pipeline requiring a “bond of trust between the generator of the data and the consumer”. The Ark also connotes a “covenant of trust with the public...”.

Likewise, decentralized governance as a concept appears in multiple places in their essay, most notably through their interesting concepts of “distributed sense making” and a “connected health city”. It is notable that the authors do envision physically centralized data stores in their connected health city model, which runs counter to the distributed models that are currently popular in the U.S.

Finally, reciprocity is multiplicatively seen in the feedback loops embedded into their “evidence pipeline” and “connected health city” concepts.

In conclusion, like the LHS itself, achievement of an LHS will be a multi-stakeholder endeavor with many partnerships among mostly like-minded but sometimes disagreeing participants showing the way. Progress requires movement from very high level concepts and values – such as those I presented at the beginning of this commentary – to more concrete models of how these concepts might be implemented in a working system. Ainsworth and Buchan have provided an important step forward in this journey.

3. Comment by A. Geissbuhler

Developing learning systems for healthcare has been one of the great challenges of medical informatics for decades, and, so far, has produced limited convincing results outside a few favorable settings. But today with, on one side, a health data deluge poised to challenge informaticians and society, and, on the other side, inflated expectations that health informatics will soon help solve healthcare access and delivery issues, there is a real need to come up with information organization models designed to face these problems.

This is precisely what Ainsworth and Buchan provide in their thoughtful paper [1]. They recognize trends, hurdles and opportunities, and provide sensible ways to organize information and knowledge in other to accelerate the emergence of learning health systems, in particular through optimized health data reuse.

In particular, their generic “evidence pipeline” model presented in the paper is useful for identifying the various roles involved in generating data and transforming it into knowledge and into meaningful use. It also facilitates the design of innovative scenarios.

In fact, this model could be further extended in order to take into account the implementation of the knowledge-enhanced decisions, the results of the derived actions, and even the impact on the outcomes, each of these additional stages apt at generating useful feedback loops.

Indeed, the execution phase of a decision and its results provides insights that may enrich or influence the whole process. As we are learning, implementation hurdles actually represent significant limitations in our ability to meaningfully deploy health information systems, especially when these reach high levels of complexity.

Fostering creativity, inclusiveness of multiple and diverse stakeholders in a heterogeneous network of information sources and systems, could seem to be an overwhelming challenge. Still, as elegantly proposed in the paper, conceptual frameworks have shown their relevance and applicability, although still mostly in limited settings. In order to span larger domains of application, and, in particular, across inter-institutional and inter-professional boundaries, the implementation of these frameworks will require significant new developments, in domain such as semantic interoperability and collaborative knowledge management. It also presents new challenges, such as varying health literacy amongst stakeholders, competing goals and values between professions and individuals, and tensions between personalization and normalization, to name but a few. These are some of the current challenges that the health informatics community should be tackling.

If successful, and, if, as the authors postulate, the combination of health data uses will ignite health system learning, setting the knowledge in motion through integration, implementation, and evaluation should then make the health system engine roar.

4. Comment by D. Kalra

Clinical care, population health, clinical trials and big data research need to operate as a single ecosystem: generating good quality data, gaining new insights from it and translating this learning into improved
and innovative health and wellness systems. These health and wellness systems encompass classical healthcare and classical social care (which have been in silos too long), patients managing conditions they have and everyone preventing conditions they don't have.

As Ainsworth and Buchan rightly highlight in their paper [1], we do not today have a coherent learning ecosystem but distinct human, organisational, technical and informational sub-systems that isolate the expertise and the data that can generate knowledge and thereby direct change. This severely limits what we can learn from the data already being collected by patients and professionals, and hampers the maturing of the "leaning health systems" that we urgently need.

The authors draw attention to the challenges facing health care provision today that makes addressing this issue so urgent, and additionally highlight the emerging opportunity of personalised medicine that critically depends on integrating and analysing the holistic information landscape of individual patients. Co-morbidity is now recognised as a major European challenge, whilst our evidence-based guidelines, care pathways and clinical team workflows primarily presume illnesses should be diagnosed, treated and managed in isolation, as if each is the only condition a patient might have.

With the growing number of even severe conditions that can be better treated and therefore now become long-term conditions, and the demographic ageing of society, comorbidity will be the norm and we urgently need the evidence – which can only be derived from analysis of comprehensive large-scale population health records – to understand how diseases and treatments interact and how to optimise multi-condition care pathways. The authors emphasise the importance of seeing this as a dynamic process of learning, in which more data from widening pools of patients and new data following every innovation in the treatment of an existing condition may alter the balance of evidence and therefore redefine the optimum care pathways.

The authors also rightly challenge the historic "one size fits all" paradigm of evidence based medicine, which bases its evidence on large sets of patients and which defines recommendations that optimise the average health status for coarse-grained disease stereotypes. The fundamental philosophy of learning from groups of patients, using statistical methods to control for random variation, remains valid, but we now have the opportunity through fine-grained electronic health records and genomics to refine and narrow the sets of patients more precisely, and thereby to improve the patient specificity of our guidelines and pathways. To realise this opportunity we need to integrate the five information pipelines identified by the authors, and make our evidence gathering and translation into practice much more agile.

The adoption of standards lies at the heart of solving the problem of combining data from heterogeneous systems and integrating these pipelines. We now have very good technical interoperability standards for the communication of clinical data between systems, but regrettably standards adoption is not strongly driven by procurements, and vendor incentives to incorporate standards into products are therefore weak. However semantic standards, that represent clinical meaning, including the clinically oriented models representing key aspects of health record documentation, are at an earlier stage of maturity and need much stronger professional engagement than we have had to date. The authors rightly emphasise the need for better interoperability between data sources, and also the importance of privacy protection and de-identification methods to enable linkage of individual records between multiple data sources whilst preserving the anonymity of those individuals. These are areas that need investment in the research and standards, as well as strong promotion of the adoption of emerging best practices – by healthcare purchaser and provider organisations, including their health ICT procurements. The authors rightly emphasise the importance of up-skilling the health and care workforces to be better able to marshal these bidirectional pipelines, for shared decision making.

The paper draws attention to the emergence of the quantified self, in which patients and healthy citizens coproduce health, information and knowledge in partnership with health professionals and other health allies, generating the evidence for new inferences (signals) that lead to better models and algorithms, and that in turn guide the individuals towards achieving better health outcomes. With the recent rush to the market of new wearable devices and mobile applications, there is presently a wave of enthusiasm about the possibilities of capturing and analysing citizen sourced data at scale. We have yet to see how and where in our ecosystem this new tidal wave of data points will yield new and valuable insights, as opposed to being simply a distraction and hype.

The Ark is an exciting concept, proposed by the authors, that brings the five pipelines together, to enhance clinical care and research. I would strongly support their assertion: "It is our belief that cross-provider pathway optimisation is a potential ignition point for system-wide learning, particularly when coupled with service planning/commissioning." The challenge that we will face in realising this vision is that a critical mass of data sources need to be combined in order to provide an initial tranche of novel insights to personalise care pathways, and an initial set of integrated health services need to be committed to implementing changes in care pathways, clinical workflows, commissioning and reimbursement models in order to achieve and showcase the benefits of the Learning Health System approach. Hopefully the Connected Health Cities in the North of England will be such a showcase.

5. Comment by M. Kimura

5.1 Reuse of Health Data in the Learning Health System

Several trials have been conducted with the aim to reuse (secondary use) health data. However, we have managed to obtain only a few full-size successes. The reasons for this are described and analysed in this paper [1], especially in section 4.2. Moreover, in section 4.4, authors have described a proposed architecture for the Learning Health System. To make full use of this architecture, the data content should be scrutinized. This comment describes what
kind of information can be used, and introduces the current trials designed to achieve them.

5.2 Health Data, with or without Context

The typical content of patient data, which are now included in health informatics systems in healthcare providers, involves prescriptions, laboratory examination results, images, and notes by professionals. Results of laboratory examinations and imaging examinations (such as concentration of chemical substances in blood samples or X-ray transparency of certain parts of a tissue) are calibrated, objective, and reproducible by technologists from each domain.

On the contrary, notes by physicians, or interpretations by professionals of a domain can have extensive background information. For example, when the extent of brain atrophy is 5%, it is considered "mild" for persons aged 80 years, while it is considered "remarkable" for those aged 30 years. The reader of the notes implicitly understands the background; however, in terms of reusing this vast amount of data, this is not taken into account. Thus, context-free data is important when considering the reuse of medical health data.

5.3 Trials Designed to Obtain Context-free Data

5.3.1 Therapeutic Area Standard of the Clinical Data Interchange Standards Consortium

The Clinical Data Interchange Standards Consortium (CDISC) is a consortium established for the development and maintenance of clinical data interchange standards, mainly for clinical research and trial use. Data for these uses comprise prescription, laboratory examination results, and notes by professionals. The CDISC, with other partners such as the Food and Drug Administration and National Cancer Institute, started developing sets of items to be used in each therapeutic area, which is known as a therapeutic area standard [10]. Alzheimer's disease, asthma, cardiovascular disease, chronic hepatitis C, diabetes, dyslipidemia, influenza, multiple sclerosis, pain, Parkinson's disease, polycystic kidney disease, QT studies, schizophrenia, tuberculosis, and virology are the current areas where standard items are published. This activity involves a standardization of items from case cards, which were ad hoc in each clinical study. Each item of the standards is clinically reproducibly defined. Through this definition, items captured for one use case can be reused in other use case.

5.3.2 Minimum Sets for Each Domain Established by the Japan Association for Medical Informatics and Partners

Many clinical research case cards are filled with several items to complete. Committee-based case cards tend to include a superset of items, and are important for each committee member. Moreover, filling side and approaching patients in busy settings, entails time and effort and thereby affects participation.

The Japan Association for Medical Informatics collaborated with four professional societies; diabetes, kidney disease, hypertension, arteriosclerosis, and four domain minimum sets were established [11]. Items included in the diabetes set are as follows: height, weight, blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, serum creatinine, urine protein, blood sugar, age at onset of diabetes, HbA1c, alanine aminotransferase, and retinopathy (only 13 items). Researchers include these items in their research case card, with, of course, additions of other important items according to their discretion. Thus, these minimum set items used in one study can be reused in other study.

5.4 Step Forward

The success of these trials depends on two factors. One is the continuous effort to keep these sets updated, clinically and technically. Another is to increase the number of context-free data items, by clarifying the possible background information of the items. Involving manpower to clarify the background, which involves additional time, does not help to increase the number of items. It would be more efficient to acquire the information automatically.

Just as standard activities themselves, being aware of other similar activities is important to avoid duplications. A forum, academic and/or technical, to exchange information regarding products is essential.

6. Comment by K. A. Kuhn

Ainsworth and Buchan [1] present an analysis of a national health system and make suggestions how to transform it into a "learning health system". Their work is interesting and relevant. I will add thoughts complementing their view and relativizing some of their statements. My first remark is a methodical one: The article is based on "stakeholder consultations" and "multiple literature reviews". While this has resulted in a good starting point for a discussion, it would have been desirable to describe the consensus process and details of a systematic literature review, e.g. search criteria and corresponding results.

My commentary will mainly consider two aspects: 1) Ainsworth and Buchan's perspective of research does not address "systems medicine", and it touches "personalized medicine" only shortly. Developments in these closely related fields, however, will massively influence healthcare and healthcare systems, and they are a relevant constituent of today's biomedical research. 2) Security and privacy challenges have not been discussed in depth. For a variety of reasons, and not least because we are entering an era of genomic medicine, security and privacy risks need to be addressed. Under an international perspective, the mentioned "opt-out" approach should be complemented.

Three "Legacy Assumptions that Impede System Learning" play an important role in the article. The authors consider them outdated but yet pervading. There are examples relativizing this, and many of them are related to personalized medicine and systems medicine (for corresponding overviews see e.g. [12, 13]). The first assumption is "Time Invariance: Assuming that Evidence is Eternal". While an example is presented in the article, there are others showing that the transient character of evi-
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Methods and systems medicine perspective, applies also for the paragraph “Technologies for innovation in health data reuse”. Regarding the sentences “Other industries/sectors have gone through a period of rapid innovations … to identify and meet the needs of their consumers/customers. Healthcare needs to learn these lessons”, I warn of considering healthcare an industry and to underestimate the changes required when experiences from other sectors are transferred.

In short, big data is primarily a technology and an enabler, whereas personalized and systems medicine are closely related to the goal of improving health care and prevention fundamentally. Patient empowerment can become a relevant constituent of an improved health system, especially when extended to the p4 perspective [19]. Security and privacy are indispensable, and their importance will even increase.

7. Comment by T. H. Payne

We find ourselves achieving many goals we have long sought: In many countries, much of the care record is now in electronic form, in massive amounts; we have immense, inexpensive computing power; understanding and technology in human genetics grows hourly. Yet despite these and the many other information riches we now enjoy, how we learn from clinical practice
is surprisingly unchanged. We hear about the potential, in airy terms such as big data and genetics revolution, and about the potential for a learning from the record of care [4]. So what is holding us back from, or slowing our progress in, the fundamental changes in how we learn to better care for ourselves and improve our health?

The simple answer is that many things hold us back, but this convenient answer doesn't focus us to action. The paper by Ainsworth and Buchan [1] does. The authors name a concept – data-action latency – to measure our progress toward a population health and care intelligence system that can support health system learning, identify barriers, and propose tests to measure progress. Improving our score on these tests will involve addressing a number of outdated assumptions and barriers that they describe in detail. This sort of characterization can awaken us, or at least invigorate those who are more cognizant, to help us begin reaping hoped-for benefits sooner, and more often.

We have growing understanding of how information traditionally considered in the domain of public health has direct importance to individual health – transportation, exercise options, and nutrition for example – and that the reverse is also true. Yet as the authors point out these are in different data streams, brought into common flow in the exceptional case, and after considerable effort. As these data sources and others grow, their potential to help – the data-action latency – grows also when they are not so used. In my clinic I use the Framingham logistic to help patients understand their options to reduce their risk of the illness that most harms Americans. Should it not be possible to understand risks for heart disease specific to them, to their city, and their lifestyle, rather than from citizens from a city in western Massachusetts? It may make a difference and we should know if it does. The same is true for their other health risks.

The authors’ analysis stimulates me to add to it: to their list of barriers I would include others. We need deeper conversation about ethics; greater public engagement; and focus on veracity of the data from which we intend to learn.

First the topic of ethics. In the U.S. over 40 years ago wise people enumerated principles to guide our government’s use of personal data, including that “there must be a way for a person to prevent information about the person that was obtained for one purpose from being used or made available for other purposes without the person’s consent” [30]. Even when there are important advantages to us all in not doing so, should we maintain this principle? Certainly it warrants awareness and discussion. Anonymization is offered as a solution but it is a spectrum, not an absolute [31], and who determines where on the spectrum we draw the line that anonymization is sufficient?

Broader public engagement includes reflecting on the value of the scientific method, which many do not understand or support. The scientific method is employed by fallible, inherently biased humans, yet it remains one of the most powerful tools we have to seek truth. Reading any newspaper reminds us that knowledge derived using the best available scientific methods, and repeatedly confirmed, still must compete with loudly voiced opinion, and often science loses, at least in the short term.

Political barriers remain, including in the U.S. the inability to create a national patient identifier to more safely and accurately link records from our mobile population to create a cohesive record of care. Concern that business or government might use such linkage for purposes counter to the individual’s interest remain in the electorate, transmitted to elected officials. There are separate funding streams and charges to public health and individual care delivery systems that complicate combining their data streams.

And of course the public expects much more than accessible, acceptable care. We expect excellence, to cure cancer, to use the newest technology with only passing consideration of (opaque) cost.

Are the records from which we might learn trustworthy? [32]. Many observations recorded in notes contain artifact of attempts to enter notes within time constraints, and note content may contain inaccuracies [33]. We do not fully know the scope of this problem. The growth of information integrity programs in the U.S. is another reflection of renewed awareness of problems with data accuracy in health IT systems [34].

There are also exceptions to the barriers enumerated in this paper that are worth highlighting. Oncologists, for example, understood earlier than most how diverse malignancy is, and that treatment can often best be delivered knowing the individual and even sub-individual variation in tumor genetics that when understood can more effectively guide treatment. This is undoubtedly true for most human maladies yet we continue to treat diverse variants as a single condition. This can, and should change.

But Ainsworth and Buchan have clearly and appropriately targeted the most important issues that we should reflect upon, and discuss with colleagues and in our communities. Their work in northwest England is also worth study and reflection within our nation. And then after reflection, we should take action to achieve the potential benefits that are within our reach to improve the health of our people.

8. Comment by F. G. B. de Quirós

The manuscript of J. D. Ainsworth and I. E. Buchan [1] is part of the current discussion of learning health systems (LHS) trying to build up a system that receives, corrects, integrates and summarizes data processing as part of the usual activities of healthcare (research, care delivery, public health and information systems).

The authors conceptualize a population health and care intelligence system capable of supporting a LHS, and put forward a set of maturity tests to progress toward such a system. They stated that the transition from data-sparse to data-intensive healthcare cannot be achieved through technologies and system management alone, as there is a major cultural change involved. This transition needs a framework and a strategy in order to succeed. Although, there are some methodological and technical aspects to discuss about the manuscript, I will discuss and focus in the conceptual aspects of theoretical framework and strategy.
LHS has been defined as one in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and healthcare [35]. LHS relies on two main concepts: learning is the basis for continuous improvement and feedback is the basis of learning. The important question here is: how to design an efficient feedback to understand population health and the healthcare system so that to build up a strategy for continuous improvement?

To analyze authors work in context, we need to consider that in all scientific/operational representation of reality (in this case population health and healthcare delivery system) there is an interaction of three basic components: 1) the observer, 2) the method used for observation and 3) the object to be observed.

There are different approaches on how this epistemological triad works in sciences and in particular in healthcare, and have been described multiple paradigms [36]. From the perspective of positivism, which asserts that "the truth" is one and an objective observer can observe and describe it as it is, or the post positivism which states that there is "one truth" but it can never be truly observed and described because the observer is influenced by its own way of looking at reality and can't be objective when observing and describing it, to the constructivism which states that there is "no one truth" as such and that it results from the collective construction of observers.

We will discuss first deeply the third part of the triad, the object to be observed i.e. "the truth". Health information systems face the challenge to represent conditions documented in the healthcare process as biological, clinical situations, preventive, diagnostic, and therapeutic options. They have information not always available such as genomics and proteomics data [37], family history or the information is not much reliable. In addition, health data is not well represented; usually Electronic Health Record has a list of disconnected entities without meaningful statements between them.

Moreover, to understand health outcomes at population level it is necessary to integrate information from other domains, for example social and behavioral data. It is well known that social environments affect human health [38]. These data as well as home and daily basis information, personal perspectives and priorities, self-documented data, among others, are often beyond the radar of "own" healthcare system. Finally, there is evidence that this information has a clear impact on health outcomes and current computerized records do not represent them well [39–41].

In summary, current information systems do not have all the variables needed to understand population health, have difficulties with semantic structure and expressivity, with the relationship between semantic concept and with the quality of biomedical data. They also have a biomedical bias because do not include all the information needed to understand the effects of the healthcare delivery system on population health.

Therefore, when we try, as authors stated, to build a system based on data that naturally arise during activities with continuous efficient feedback for an efficient improvement, we must clearly define if we want to assess and improve the functioning of care delivery system or pretend to understand the impact of the care delivery system on population health. If we want to assess and improve the functioning of healthcare, the system will have much of the information to answer the question. However, we should redefine the sources and types of data to understand the impact of the care delivery system on population health.

Solving this dilemma and assuming we can effectively access to information that describes the object we want to observe, understand and describe, we must resolve the issues raised by the authors. The special focus should be on the barriers to use the described and the proposed technologies for innovation in health data reuse, in particular, data analytics. Authors also propose a very comprehensive conceptual framework with bidirectional evidence pipelines, to population health e-Lab model for ground connection between evidence and the evidence and person-accountable decision-making at all levels (population/system, clinical and self-care) in order to take care of the four “Vs” (Volume, Velocity, Variety and Veracity) of data. For adding value to the system the authors’ proposal includes access to quality and timely information and above all tries to gather more expressiveness from the original information and not to suffer in this process multiple semantic aggregations amendments that remove wealth.

If those technical aspects were solved it is worth ask about the first part of the triad; If the observers will have the objectivity and enough understanding to see what data is representing and adding the least amount of personal, professional and social biases. Or we might consider that if we try to understand population health and in particular the “why question” of the decision of professionals and citizens, the observer cannot be totally objective, the reality is complex and partially constructed by personal and social relationships and behaviors.

If this is the case, we might have to analyze the second part of the triad; the methods used to observe and describe this reality. Population health and health care are open sociocultural systems with interdependence between their components; people have self-organization and freedom of choice. These are three components that determine chaotic or complex systems [42]. In these kind of systems one “action or stimulus” provokes nonlinear and perhaps different “consequences” depending on the quality of associativity between them and how the different components (healthcare professionals, citizens, etc.) relate each other. Pieces of a “socio-cultural system” are not mechanistic pieces with predictable response. They “think and decide” each time. In this context, linear logic of cause and effect it is not enough to understand the whole reality.

In this scenario, the paradigm used in social and behavioral science and in particular in personal and social learning processes [43] also involves LHS projects. This strategy requires to seek new computer systems with non-reductionist representation; nonlinearities and discontinuities; aggregate macroscopic patterns rather than causal microscopic events; probabilistic
rather than deterministic outcomes and predictions; change rather than stasis [44]; where data stored "do not speak by itself" and systems facilitate human consideration and learning in a constructive interactively way tailored to each social and historical context and ground [45].

9. Comment by J. C. Wyatt

Ainsworth and Buchan propose an interesting vision of a future in which clinical data are readily reused to support rapid-cycle continuing quality improvement – the Learning Healthcare System [1]. This is similar to the idea of a Knowledge Commons for Health [46]. A key question is, does this mechanism supplement or replace the conventional clinical research process, with its paraphernalia of randomised trials, ethical approval and systematic reviews? While they suggest that most conventional research results do not endure so that constant updating is needed, their only example is of cardiac risk prediction models. This of course is an area in which prognosis has changed dramatically in the last few decades, with mortality rates now less than half what they were in the early 1980s in many countries [47]. Other important kinds of clinical knowledge – such as drug effect sizes from systematic reviews – have changed much less. Another potential criticism of randomised trials is that some are limited by over comprehensive inclusion criteria to study only small percentages of those patients who were screened for eligibility. However, this has been changing since Peto’s call in 1978 for “Large, simple trials” [48], and there is now much focus on pragmatic trials, with a 2008 reporting guideline and checklist, Practich to assess how pragmatic a trial is [49]. So, evidence-based medicine, trials and systematic reviews still have a place even in the multiply-connected world of Learning Health Systems, as predicted by Byar in his seminal 1980 paper [50], “Why databases should not replace trials”; and revisited by Liu in 2011 [51].

Table 1 explores some of the distinguishing features between the learning healthcare system and the evidence based approaches to answering health related questions.

In addition to conventional RCTs, as Ainsworth and Buchan point out, new forms of trial are emerging. They mention N of 1 trials which again date back to the 1980s [52], but whose adoption in the UK and some other countries has been delayed by confusing ethical guidance that states that any randomisation implies research, so must be regulated as such [53]. The aim of an N of 1 trial is to tailor treatment to an individual's needs, so it hardly aims to produce generalizable knowledge – the hallmark of research. Another variation on the standard RCT is the point of care ran-

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Learning Healthcare System</th>
<th>Evidence Based approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>Generating useful insights to inform local decisions</td>
<td>Creating generic knowledge; testing theories</td>
</tr>
<tr>
<td>Philosophical basis</td>
<td>Pragmatism, trial &amp; error</td>
<td>Positivism</td>
</tr>
<tr>
<td>Scope</td>
<td>Local / regional health economy</td>
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</tr>
<tr>
<td>Approach to managing context</td>
<td>Included in the evaluation</td>
<td>Excluded from the evaluation (assumed to be much less important than the intervention)</td>
</tr>
<tr>
<td>Timing of the insights generated</td>
<td>Cyclical (weeks / months to answer)</td>
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</tr>
<tr>
<td>Perspective</td>
<td>Forward from the present</td>
<td>Backwards</td>
</tr>
<tr>
<td>Main threats</td>
<td>Spurious associations, biased data or comparisons (eg. confounding by indication)</td>
<td>External validity, Insights expire over time</td>
</tr>
<tr>
<td>Who pays, and cost drivers</td>
<td>Healthcare infrastructure, driven by costs of data capture, analytics</td>
<td>Research funders, driven by costs of recruitment, consent, data capture &amp; analysis</td>
</tr>
<tr>
<td>Process model</td>
<td>Continuous flow</td>
<td>Batch production</td>
</tr>
<tr>
<td>Who leads the process</td>
<td>Healthcare professionals, healthcare delivery organisations</td>
<td>Academics, healthcare professionals, universities</td>
</tr>
<tr>
<td>Source of the questions studied</td>
<td>The local healthcare system</td>
<td>Research funders, national consultations, systematic reviewers and guidance developers (research gaps)</td>
</tr>
<tr>
<td>Local buy-in to the study results</td>
<td>Probably high</td>
<td>May be low</td>
</tr>
<tr>
<td>Regulation &amp; consent</td>
<td>Nil apart from regulations governing the use of personal data for continuing quality improvement</td>
<td>EU Clinical Trials Directive, local research governance and ethical oversight for enrolment in trials; nil for systematic reviews</td>
</tr>
<tr>
<td>Summary</td>
<td>Rapid cycle learning &amp; approximation to what works</td>
<td>Slow, rigorous assessment of effect sizes, prognostic factors, etc.</td>
</tr>
</tbody>
</table>

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domised trial described by van Staa et al [55], in which people with a common clinical problem whose solution is unknown are routinely randomised to the best current alternatives. Due to a misunderstanding of their aims, complex ethical and research governance issues can arise here, even when the intent is to simply resolve an important clinical dilemma between two commonly used drugs [54]. Surely when there is genuine equipoise, the only responsible action is a low risk RCT, rather than the continuing medical muddle that results from individual chaotic decisions that, because of confounding by indication [50], prevent reliable causal inference from routine data? It is the lack of a suitable trial that inhibits personal autonomy and the right to the best treatment, rather than the automatic recruitment that point of care trials entail. It is notable that several major global funders such as the World Bank & Gates Foundation now endorse RCTs as the most efficient way to establish the benefits and risks of interventions as varied as mass vaccination or cash supplements to families subsisting below the poverty line. And industry uses randomisation routinely, without asking for our consent, to constantly improve their e-commerce and social media websites [55]. So, we need to revisit EU and national guidance on randomised trials to ensure that we allow – and even encourage – the conduct of low risk trials using existing agents that are already licensed that are carried out to improve clinical practice, rather than for commercial purposes. This kind of rigorous experiment designed to generate transferable, enduring knowledge can be facilitated by, and is complementary to, the locally relevant insights produced by the learning healthcare system approach.

We must also ensure that there is space in our new learning health systems for tools that encourage experimentation by recruiting patients to pragmatic randomised studies [54] and collecting unobtrusive outcome data, to ensure that comparisons are not biased by Simpson’s Paradox [56] or other sources of confounding. Perhaps the question we should defend is, what is the difference between trial and error combined with learning from our mistakes, data-driven quality improvement and “research” that focusses on answering genuine clinical or policy dilemmas, as long as we use the lowest risk and most efficient means to answer it? Sometimes that will be a pragmatic, point of care trial, sometimes a series of N of 1 experiments, while other times the best solution may be A-B testing or instrumental variable graphical inference models. Finally, maybe it is time to relabel all of these activities “service improvement”, losing the automatic requirement for ethical & research governance approval associated with randomisation as long as the question originates from (or has been sanctioned by) a health system – rather than being carried out merely to embellish the investigator’s curriculum vitae – or a company’s balance sheet.

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Addresses of the Authors

Spiros Denaxas
Institute of Health Informatics
University College London
222 Euston Road
London NW1 2DA
United Kingdom
E-mail: s.denaxas@ucl.ac.uk

Charles P. Friedman
Department of Learning Health Sciences
University of Michigan, Medical School
1111 E. Catherine St.
Ann Arbor, Michigan 48109
USA
E-mail: cpfried@umich.edu

Antoine Geissbuhler
University of Geneva
Department of Radiology and Medical Informatics
Rue Gabrielle-Perret-Gentil 4
1211 Genève 14
Switzerland
E-mail: Antoine.Geissbuhler@hcuge.ch

Harry Hemingway
Institute of Health Informatics
University College London
222 Euston Road
London NW1 2DA
United Kingdom
E-mail: h.hemingway@ucl.ac.uk

Dipak Kalra
The EuroRec Institute
c/o University Hospital of Ghent
Building 3, 5th Floor
De Pintelaan 185
9000 Gent
Belgium
E-mail: dipak.kalra@eurorec.org

Michio Kimura
Hamamatsu University School of Medicine
Department of Medical Informatics
1–20–1 Handa, Hamamatsu 431–3192
Japan
E-mail: kimura@mi.hama-med.ac.jp

Klaus A. Kuhn
Technische Universität München
Klinikum rechts der Isar
Institute of Medical Statistics and Epidemiology
Ismaninger Str. 22
81675 München
Germany
E-mail: klaus.kuhn@lrz.tu-muenchen.de

Thomas H. Payne
University of Washington
Department of Medicine
UW Medicine IT Services
Box 359968
325 Ninth Ave
Seattle WA 98104-2499
USA
E-mail: tpayne@u.washington.edu

Fernán González Bernaldo de Quirós
Hospital Italiano de Buenos Aires
Buenos Aires
Argentina
E-mail:
fernan.quiros@hospitalitaliano.org.ar

Jeremy C. Wyatt
University of Leeds
Leeds Institutes of Health Sciences and Data Analytics
Charles Thackrah Building
101 Clarendon Road
Leeds, LS2 9LJ
United Kingdom
E-mail: J.C.Wyatt@leeds.ac.uk
From 2016–01–01:
University of Southampton
Wessex Institute of Health
Alpha House, Enterprise Road
Southampton, SO16 7NS
United Kingdom