Pharmacogenomics in the pocket of every patient? A prototype based on Quick Response (QR) codes.

Matthias Samwald [a,b], Klaus-Peter Adlassnig [a,c]

[a] Section for Medical Expert and Knowledge-Based Systems, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria

[b] Information & Software Engineering Group, Institute of Software Technology and Interactive Systems, Vienna University of Technology, Vienna, Austria

[c] Medexter Healthcare GmbH, Vienna, Austria

Corresponding author
Dr. Matthias Samwald

Spitalgasse 23
BT 88.03
1090 Vienna
Austria

matthias.samwald@meduniwien.ac.at
Tel.: +43 699 811 68 028
Fax: +43 1 40400 6667

Keywords
pharmacogenetics, personalized medicine, clinical decision support systems, barcode technology, mobile devices

Word count
1917

Abstract

A sizable fraction of patients experiences adverse drug events or lack of drug efficacy. A part of this variability in drug response can be explained by genetic differences between patients. However, pharmacogenomic data as well as computational clinical decision support systems for interpreting such data are still unavailable in most healthcare settings. We address this problem by introducing the Medicine Safety Code (MSC) which captures compressed pharmacogenomic data in a two-dimensional barcode that can be carried in a patients' wallet. We successfully encoded data about 385 genetic polymorphisms in MSCs and were able to quickly decode and interpret MSCs with common mobile devices. The MSC could make individual pharmacogenomic data and decision support available in a wide variety of healthcare settings without the setup of large-scale infrastructures or centralized databases.

Objective

A sizable fraction of patients undergoing drug treatment experiences adverse drug events or a lack of positive effects. A part of this variability in drug response can be explained by genetic differences between patients, which can strongly influence how medications are metabolized or are able to bind to their targets (pharmacogenomics). Genetic testing is rapidly becoming affordable, and some companies started offering tests with single nucleotide polymorphism (SNP) microarrays for less than 300 Dollars per person (1). When pharmacogenomic data of a patient is made available to physicians, it can significantly alter their prescribing behaviour and lead to reduced hospitalization rates (2). Still, there are several issues that need to be addressed:

1. *Problems with integrating genetic testing into routine medical care:* For common medications where pharmacogenomic effects might be relatively subtle, the delay and financial overhead incurred by genetic testing prior to initiating treatment might not be deemed acceptable. Furthermore, severe adverse drug effects might occur rapidly after treatment initiation in

some cases (3). These issues might be better addressed through prospective pharmacogenomic testing, i.e., having pharmacogenomic patient data readily available when needed without delays or additional costs.

2. *Lack of efficient and widely accepted storage mechanisms:* Interoperable electronic health records supporting pharmacogenomic data remain unavailable in major parts of the world, even though rapid advances are being made in some regions (4). Furthermore, genetic data are explicitly excluded from health records in some regions because of privacy concerns – for example, legal regulations in Austria disallow capturing personal genetic data in the country-wide electronic health record infrastructure.
3. *Lack of computational clinical decision support:* Effective computational clinical decision support is required to make pharmacogenomic data useful for medical professionals. While some institutions are already spearheading the use of pharmacogenomic data to generate automated alerts and reminders (4–6), pharmacogenomic decision support remains unavailable in the health care system at large.

In this paper we address these issues by presenting a prototype of the Medicine Safety Code technology (http://safety-code.org/), a light-weight approach to improving the availability and the interpretation of individual pharmacogenomic data in routine medical care.

Figure 1: An example of a Medicine Safety Code.

A Medicine Safety Code (MSC) is a standardized two-dimensional (2D) barcode that captures key pharmacogenomic traits of an individual patient. An example of an MSC is shown in Figure 1. The 2D barcode is based on the Quick Response (QR) code standard (7) that was published by Toyota in 1994. QR codes have recently become widely popular due to their fast readability, high information density and the ability to contain hyperlinks to pages on the World Wide Web.

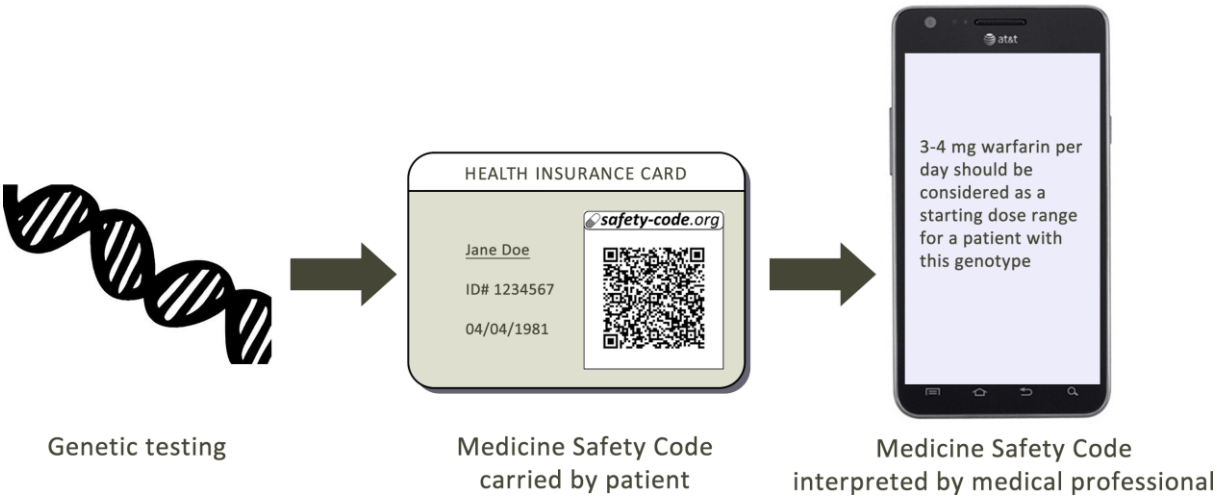

Figure 2: A personal Medicine Safety Code can be generated from genetic test results and printed on a card carried in a patient's wallet. The Medicine Safety Code can be quickly decoded with common mobile devices, offering computer-based pharmacogenomic decision support services to medical professionals.

Like any QR code, MSCs can be printed on paper and can be included in lab reports, paper-based health records or small cards that can be carried by patients in their wallets (Figure 2). MSCs can be decoded with common smartphones and other devices to yield a string in the form of a Uniform Resource Locator (URL). This string has a two-fold role: First, it contains the compressed, anonymous pharmacogenomic data of the individual. Using specialized software, these data can be decompressed and interpreted without requiring any Internet or database access (this is an important difference to most common uses of QR codes). Second, when the URL is resolved with a standard web browser, the MSC web server decodes the data contained in the URL and generates a report, including quick access to clinical decision support algorithms that can help medical professionals optimize care based on the individuals' pharmacogenomic data. This second option makes it possible to decode and use MSCs with common smartphones, without necessitating the roll-out of a dedicated IT infrastructure for pharmacogenomic data storage, retrieval and interpretation.

This simplicity and flexibility of the MSC could make pharmacogenomic data available and actionable in a multitude of healthcare settings.

Materials and Methods

The set of single nucleotide polymorphisms captured by the MSC was compiled by merging lists of pharmacogenes and their polymorphisms from existing pharmacogenomics datasets. The following sources were used (based on snapshots of the source data taken in February 2012):

a) The list of 'very important pharmacogenes' and their associated SNPs hosted by the Pharmacogenomics Knowledge Base (PharmGKB) (8,9)
b) The PharmaADME core gene list (10)
c) Markers mentioned in FDA drug labels that were not already covered by PharmGKB or PharmaADME (excluding markers for mutations in cancer tissue)

Web services for encoding, decoding and interpreting MSCs were made publicly available under the http://safety-code.org/ domain. The service for decoding and interpreting is called automatically when an MSC code is scanned with a mobile device. The current prototype offers CDS recommendations for warfarin dosing, and shows raw data for all genetic markers.

We conducted a simple proof-of-concept test for evaluating the general plausibility of the technology with MSCs printed on pocket-sized cards. The ease and speed of decoding the MSCs was tested with a common smartphone (Galaxy Nexus, Samsung Group) with a camera sensor resolution of 5 Megapixels and a pre-installed QR code reader application ('Google Goggles'). The authors measured the minimal time needed from picking up a card with a printed MSC until viewing the individual recommendation for warfarin dosing.

Results

Merging the key pharmacogenes listed in PharmGKB, PharmaADME and FDA drug labels yielded a list of 58 pharmacogenes with 385 associated polymorphic loci (Table 1). The list includes several

enzymes from the cytochrome P450 family, which are determinants of the pharmacokinetics of most common medications.

Table 1: The key pharmacogenes of which variants can be encoded in a Medicine Safety Code. The number of different markers captured for each gene is listed in brackets. In total, 385 markers of polymorphic loci associated with 58 genes are captured.

ABCB1 (7), ABCC2 (6), ABCG2 (1), ACE (1), ADRB1 (2), ADRB2 (3), AHR (1), ALOX5 (1), BRCA1 (16), COMT (4), CYP1A1 (4), CYP1A2 (20), CYP2A6 (12), CYP2B6 (36), CYP2C19 (37), CYP2C8 (4), CYP2C9 (20), CYP2D6 (16), CYP2J2 (1), CYP3A4 (13), CYP3A5 (15), DPYD (15), DRD2 (4), F5 (1), G6PD (6), GSTM1 (1), GSTP1 (2), HLA-B*1502 (2), HLA-B*5701 (1), HMGCR (11), IL28B (1), KCNH2 (5), KCNJ11 (1), MTHFR (2), NAT1 (7), NAT2 (8), NQO1 (2), NR1I2 (1), P2RY1 (2), P2RY12 (4), PTGIS (1), PTGS2 (3), SCN5A (3), SLC15A2 (4), SLC19A1 (5), SLC22A1 (9), SLC22A2 (5), SLC22A6 (1), SLCO1B1 (22), SLCO1B3 (2), SLCO2B1 (1), SULT1A1 (3), TPMT (5), TYMS (2), UGT1A1 (11), UGT2B15 (1), UGT2B7 (1), VKORC1 (10)

QR codes of different sizes could be readily decoded with the testing device used. Even compact QR codes with a side length of only 1,15 cm (Figure 3) were quickly recognized when holding the camera at a distance of about 10-15 cm from the code. However, older smartphone devices with lower camera resolutions and poorer ability for taking pictures at short distances will require larger QR code sizes to ensure successful decoding.

Figure 3: An example of a printed MSC. The QR code in this example had a side length of 1,15 cm and was readily decoded with the smartphone device used for proof-of-concept testing.

When using QR codes with a side length of 1,15 cm, the minimum time needed to pick up a card with a printed MSC, decode the QR code, select warfarin among the list of available medications and display the warfarin CDS message (Figure 4) was around 15 seconds.

Figure 4: An example of the online clinical decision support algorithms available through the Medicine Safety Code server. Through this service, a patient's Medicine Safety Code can be read and interpreted by most common smart phones without requiring the installation of dedicated software.

Discussion

To our knowledge, the MSC is the first technology that has the potential to make individual pharmacogenomic data and decision support available in a wide variety of healthcare settings without the setup of large-scale IT infrastructures or centralized databases.

Potential benefits

Patients and medical professionals could profit from a reduction of adverse drug events, improvement of effectiveness of treatment, improved transparency, privacy and individual control over data, as well as international availability of the system. Health insurance organisations could benefit from reduced costs associated with adverse drug events and lacking effectiveness, fewer genetic testing and fewer follow-up visits. It needs to be evaluated if such cost reduction could offset

the cost of wide-spread genetic testing and the creation of MSCs. It also needs to be assessed which patient groups should receive genetic testing, and when.

Improved availability of pharmacogenomic data in clinical routine could also harbour potential benefit for the pharmaceutical industry. Many promising drugs fail at late stages of clinical trials because of insufficient efficacy or safety in a broadly defined patient population. When both clinical trial designs and drug prescription practices can take individual pharmacogenomic markers into account it could be possible to bring drugs to market that would otherwise have failed requirements for safety.

Limitations and potential disadvantages

The most obvious technical limitation lies in the limited number of genetic traits and other data items that can be encoded in a QR code of any reasonable size. While all key pharmacokinetic genetic markers can currently be captured – and this list is likely to remain relatively stable throughout the next few years – it might nonetheless prove too limited in the long term. We expect that the current technology cannot contain data on more than 500-600 polymorphisms. However, these constraints may be addressed by further improvements in data compression, as well as by capturing alleles/haplotypes instead of fine-grained data items such as SNP variants. It should also be noted that a low-cost genotyping array geared towards clinical pharmacogenomics was recently developed, which tests for 256 polymorphisms (11). Data from such an array could easily be captured in an MSC with the current approach.

A significant barrier to adoption is that the MSC technology requires changes to existing medical workflows during medication prescription or dispensing. It has been shown that a good integration into existing workflows is a prerequisite to the success of clinical decision support systems (12).

Data security and privacy

The security and privacy of personal genetic data are reason for heavy concern among patients and medical professionals alike. Even though the relatively small set of genetic markers used by the MSC

is only of limited value for determining disease risk, it could still be used as a biological 'fingerprint', making it possible for forensic labs to identify persons based on minute amounts of biological samples. The collection of such genetic fingerprints in large centralized repositories such as national electronic health record systems would likely be met by strong public opposition. The MSC technology provides a possible solution to this problem, since no centralized collection and storage of personal genetic data is necessary. Patients can be given full control over their genetic data, just as they have full control over the content of their wallets. Some security and privacy issues remain to be further analysed, such as the possibility of unwanted scanning of MSCs by third parties.

Related work

A rapid, bedside pharmacogenomic assay for testing the presence of variants of the CYP2C19 gene has recently become available. This assay can generate results within 60 minutes, and preliminary clinical tests in patients undergoing angioplasty showed positive results (13). While this approach seems feasible for high-risk scenarios in inpatient settings, it is currently not clear if it will be applicable to commonly prescribed medications and outpatient settings. Pilot projects that integrate pharmacogenomic data in electronic health records have also been documented (5,6).

Several biomedical applications of QR codes have been proposed recently, such as using QR codes for accurately transmitting prescription data from hospitals to pharmacies (14), providing paramedics with a link to a patient database with personal health histories and allergies in case of an emergency (15,16) and DNA barcoding of animal and plant species (17).

Future work

More clinical decision support rules need to be curated and formalized. User testing with medical professionals needs to be done to evaluate and improve the practicality of the technology. Eventually, future versions of the MSC technology need to be evaluated in clinical trials.

The work presented in this paper is conducted in the context of the World Wide Web Consortium (W3C) Health Care and Life Science Interest Group (18) and we plan to integrate these developments

with related work of this group (19–21). To ensure interoperability with forthcoming electronic health record systems, we will work on connecting the MSC to relevant Health Level 7 (HL7) standards and the Logical Observation Identifiers Names and Codes (LOINC) database.

Conclusion

The introduction of low-cost genetic testing combined with effective computational clinical decision support holds great potential for improving the safety and effectiveness of pharmacotherapy. We hope that the work presented here can help in realizing this potential.

Acknowledgements

We thank Simon Lin, Harold Ye, Russ Altman, Joanne Luciano, Michel Dumontier, M. Scott Marshall, Robert Freimuth and Richard Boyce for their valuable feedback.

Competing interests

The authors declare no competing interests.

Funding

This work was supported in part by the Medical University of Vienna and by the Medicine Safety Code initiative.

References

1. Genetic Testing for Health, Disease & Ancestry - 23andMe [Internet]. [cited 2012 Apr 11]. Available from: https://www.23andme.com/

2. Epstein RS, Moyer TP, Aubert RE, OKane DJ, Xia F, Verbrugge RR, et al. Warfarin Genotyping Reduces Hospitalization Rates: Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study). Journal of the American College of Cardiology. 2010 Jun 22;55(25):2804–12.

3. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. New England Journal of Medicine. 2004;351(27):2827–31.

4. Swen JJ, Wilting I, Goede A de, Grandia L, Mulder H, Touw DJ, et al. Pharmacogenetics: From Bench to Byte. Clinical Pharmacology & Therapeutics. 2008 May 1;83(5):781–7.

5. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, et al. Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project. Clinical Pharmacology & Therapeutics. 2012;92(1):87–95.

6. Swen JJ, Nijenhuis M, Boer A de, Grandia L, Zee AHM der, Mulder H, et al. Pharmacogenetics: From Bench to Byte - An Update of Guidelines. Clinical Pharmacology & Therapeutics. 2011 Mar 16;89(5):662–73.

7. QR Code.com [Internet]. [cited 2012 Jul 17]. Available from: http://www.qrcode.com/en/aboutqr.html

8. McDonagh EM, Whirl-Carrillo M, Garten Y, Altman RB, Klein TE. From pharmacogenomic knowledge acquisition to clinical applications: the PharmGKB as a clinical pharmacogenomic biomarker resource. Biomark Med. 2011 Dec;5(6):795–806.

9. The Pharmacogenomics Knowledge Base [PharmGKB] [Internet]. [cited 2011 Oct 3]. Available from: http://www.pharmgkb.org/

10. www.pharmaadme.org - Home [Internet]. [cited 2012 Apr 19]. Available from: http://www.pharmaadme.org/

11. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing Personalized Medicine: Development of a Cost-Effective Customized Pharmacogenetics Genotyping Array. Clin. Pharmacol. Ther. [Internet]. 2012 Aug 22 [cited 2012 Sep 13]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22910441

12. Kawamoto K. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ. 2005 Apr;330(7494):765–0.

13. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. The Lancet. 5;379(9827):1705–11.

14. Lin C-H, Tsai F-Y, Tsai W-L, Wen H-W, Hu M-L. The feasibility of QR-code prescription in Taiwan. J Clin Pharm Ther. 2012 Dec;37(6):643–6.

15. Lifesquare [Internet]. [cited 2012 Jul 17]. Available from: https://www.lifesquare.com/

16. ScanMed QR : Medical Alert QR Bracelets & ID Technology - ScanMed QR [Internet]. [cited 2012 Nov 22]. Available from: http://scanmedqr.com/

17. Liu C, Shi L, Xu X, Li H, Xing H, Liang D, et al. DNA Barcode Goes Two-Dimensions: DNA QR Code Web Server. PLoS ONE. 2012 Mai;7(5):e35146.

18. HCLSIG - ESW Wiki [Internet]. [cited 2012 Nov 26]. Available from: http://esw.w3.org/topic/HCLSIG

19. Samwald M, Coulet A, Huerga I, Powers RL, Luciano JS, Freimuth RR, et al. Semantically enabling pharmacogenomic data for the realization of personalized medicine. Pharmacogenomics. 2012 Jan;13(2):201–12.

20. Samwald M, Stenzhorn H, Dumontier M, Marshall MS, Luciano J, Adlassnig K-P. Towards an interoperable information infrastructure providing decision support for genomic medicine. Stud Health Technol Inform. 2011;169:165–9.

21. Samwald M, Jentzsch A, Bouton C, Kallesoe CS, Willighagen E, Hajagos J, et al. Linked open drug data for pharmaceutical research and development. J Cheminf. 2011;3(1):19.