Review

Blockchain distributed ledger technologies for biomedical and health care applications

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ABSTRACT

Objectives: To introduce blockchain technologies, including their benefits, pitfalls, and the latest applications, to the biomedical and health care domains.

Target Audience: Biomedical and health care informatics researchers who would like to learn about blockchain technologies and their applications in the biomedical/health care domains.

Scope: The covered topics include: (1) introduction to the famous Bitcoin crypto-currency and the underlying blockchain technology; (2) features of blockchain; (3) review of alternative blockchain technologies; (4) emerging nonfinancial distributed ledger technologies and applications; (5) benefits of blockchain for biomedical/health care applications when compared to traditional distributed databases; (6) overview of the latest biomedical/health care applications of blockchain technologies; and (7) discussion of the potential challenges and proposed solutions of adopting blockchain technologies in biomedical/health care domains.

Key words: blockchain, distributed ledger technology, health information exchange, security, interoperability

THE BITCOIN BLOCKCHAIN

The Bitcoin crypto-currency

One of the best-known applications of blockchain is the crypto-currency Bitcoin (in this article, we use “Bitcoin” to indicate the currency and “bitcoin” to denote the actual digital coins).1,2 Bitcoin was proposed by the unidentified person or persons “Satoshi Nakamoto” (which is speculated to be a fake name) through a famous white paper1 published in October 2008. In the following year, the open-source Bitcoin implementation was released.2 As a peer-to-peer digital currency without a central administrator, Bitcoin is categorized as a decentralized virtual currency by the US Treasury.3 Bitcoin has the unofficial ISO-4217 currency code XBT, which is used by organizations and companies such as Bloomberg4 and XE.5 The unit of Bitcoin is BTC, and 1 BTC is equivalent to about 1200 US dollars as of April 2017.6 Currently, Bitcoin has the highest total market value (19 billion US dollars or 16 million BTC, as of April 2017) among >100 various crypto-currencies currently being used.7

Bitcoins (BTCs) can now be used online at electronic commerce websites to purchase a wide range of commodities and services (see Supplementary Appendix Section A.1 for more details).8–11

Known challenges for crypto-currencies: double-spending and single-point-of-failure

The underlying distributed ledger technology of Bitcoin is also indicated as the Bitcoin blockchain, to distinguish it from other blockchain technologies. The original motivation of the Bitcoin blockchain technology was to solve the peer-to-peer double-spending problem (Figure 1).1 How can we prevent electronic coins (defined as “a chain of digital signatures”) such as bitcoins from being spent twice without having a central intermediary (eg, bank or mint)?

It should be noted that the central intermediary is not desired because it creates a single-point-of-failure, as shown in Figure 2A.12 That is, if the central intermediary is down for any reason, including scheduled maintenance, the entire network system stops. Also, if the
central intermediary is intruded upon (e.g., the administrator account is compromised), the whole network faces the invasion risk. Therefore, a decentralized network topology, as shown in Figure 2B, would be more desirable to avoid such a single-point-of-breach.

The Bitcoin blockchain solution: hash-chain timestamping and proof-of-work algorithm

To solve the double-spending problem, each computation node in the blockchain network not only needs to store every transaction to enable the distributed verification of the transactions, but also to follow a distributed timestamp mechanism to determine which transactions should be accepted and which should be rejected, as shown in Figure 2C. The Bitcoin blockchain exploits hash-chain as a distributed timestamp mechanism, and every node maintains a copy of the chain to store every transaction (Figure 3).

Additionally, the “mining” process (i.e., creating a block with enclosed transactions) should be relatively difficult to do, but relatively easy to check. The process should be difficult (i.e., time-consuming and costly) in order to make attempts to create invalid blocks prohibitively expensive (at the cost of increasing the time available to create valid blocks). To implement such a design, Bitcoin blockchain adopts a proof-of-work protocol that each block creator has to follow. Figure 4 illustrates how a chain of blocks is created with this protocol.

A detailed benefit of the proof-of-work consensus protocol used in blockchain is the ability to resolve disagreement of the chains, and thus let blockchains be immutable audit trails. That is, when an attacker modifies a block, all the blocks after that block are recomputed, because each block contains the hash value of the previous block’s header, and the computational cost of such modification should be high enough to prohibit attacks (Figure 4).

On the other hand, when an attacker creates a malicious chain to compete with an honest chain and tries to replace the honest one, the proof-of-work majority voting mechanism can also significantly reduce the probability of such an attack to succeed (Figure 5). Detailed analyses of the attack-resisting ability of the blockchain proof-of-work consensus protocol are proposed in several recent studies. The Bitcoin mechanism also provides rewards to the nodes, as an incentive to compensate the high cost associated with “mining” a new block and verifying transactions (see Supplementary Appendix Section A.2 for more details).

ALTERNATIVE BLOCKCHAIN TECHNOLOGIES AND BLOCKCHAIN APPLICATIONS BEYOND THE FINANCIAL DOMAIN

Alternative crypto-currencies and blockchains

After Bitcoin, many other crypto-currencies, such as Ethereum (4 billion USD market cap), Ripple (1 billion USD market cap), Dash (534 million USD market cap), Litecoin (512 million USD market cap), and Monero (311 million USD market cap) were developed. Additionally, several alternative blockchains (or “altchains”) have been proposed (such as Colored Coins and Sidechains) and are considered to be blockchain 1.0 technologies. Several alternative protocols to the proof-of-work (see the example shown in Figure 4)
have also been proposed, such as proof-of-stake, where the node with oldest coins can create a new block; proof-of-burn, where the node willing to “burn” or destroy the largest number of coins, by sending it to a “NULL” address, can create a new block; and proof-of-elapsed-time, where the node with the shortest wait time verified by the trusted execution environment can create a new block.

**Blockchains as distributed ledgers**

Although blockchain was originally designed as a crypto-currency, it is also regarded as a new form of the distributed database or ledger, as arbitrary data can be stored in the metadata of the transactions. Bitcoin blockchain supports metadata since 2014. The original Bitcoin blockchain only supports 80 bytes of metadata, but other blockchain implementations support larger sizes. For example, MultiChain supports metadata with adjustable size, and BigchainDB has no hard limit on metadata size.

A blockchain-based distributed ledger is also known as blockchain 2.0, including the new technologies of “smart properties” and “smart contracts.” The former refers to the digital properties with ownership controlled by blockchain, and the latter refers to the computer programs designed to manage smart properties. One of the most well-known smart property/contract systems is Ethereum, which is a decentralized platform for smart contracts. Ethereum as a cryptocurrency itself also has the second-largest market cap as of April 2017. Microsoft adopted Ethereum as the core of its new Blockchain-as-a-Service on the Azure cloud computing environment. Additional distributed ledger blockchains are described in Supplementary Appendix A.3.

**Nonfinancial applications for the original and alternative blockchain technologies**

Recently, the idea of blockchain 3.0 has been proposed to denote nonfinancial applications of the distributed ledger technology. For example, Namecoin applies Bitcoin technology to Domain Name Server and identity management. Another example is to apply blockchain in the scientific research cycle (eg, funding, experiment, analysis, publication, etc.), as blockchain is decentralized, distributed, immutable, and transparent. These applications are implemented either as permissionless (ie, any user can participate) or permissioned (ie, only authorized institutions or researchers can participate) blockchain networks.
Although blockchain technologies such as Bitcoin blockchain are widely recognized and have been used for several purposes, in health care they became known as a means to pay ransom for institutions that had their data “kidnapped” (ie, encrypted by malicious users who request payment to unencrypt the data).\textsuperscript{51,63} Ransomware has affected several health care systems, resulting in thousands of dollars in known ransom payments so far. Bitcoin currency is used because it is reliable, while it is very difficult to track its recipient. The technology behind Bitcoin, however, can be used to help instead of harm health systems and biomedical research.

**KEY BENEFITS OF BLOCKCHAIN WHEN COMPARED TO TRADITIONAL DISTRIBUTED DATABASES FOR BIOMEDICAL/HEALTH CARE APPLICATIONS**

To better understand why blockchain distributed ledger technology may be feasible for biomedical and health care applications, we describe the key benefits or comparative advantages of blockchain\textsuperscript{45,46,63-65} by comparing it with the traditional distributed database management system (DDBMS),\textsuperscript{66,67} such as Structured Query Language (SQL)-based systems like Oracle\textsuperscript{68} and NoSQL-based systems like Apache Cassandra.\textsuperscript{69}

The first key benefit of blockchain is decentralized management. DDBMSs are logically centralized-managed (ie, users logically feel they are operating a centralized database, but the underlying machines can be physically distributed), while blockchain is a peer-to-peer, decentralized database management system (ie, each node runs independently while following the protocols).\textsuperscript{45,63,64} Therefore, blockchain is suitable for applications where independently managed biomedical/health care stakeholders (eg, hospitals, providers, patients, and payers) wish to collaborate with one another without ceding control to a central management intermediary.\textsuperscript{13,45,65}

The second key benefit is the immutable audit trail. DDBMSs support create, read, update, and delete functions like all database systems, while blockchain only supports create and read functions (ie, it is very difficult to change the data or records).\textsuperscript{45} Thus, blockchain is suitable as an unchangeable ledger to record critical information (eg, insurance claim records).

The third is data provenance. On DDBMS, the ownership of digital assets can be modified by the system administrator, while on blockchain, the ownership can only be changed by the owner, following the cryptographic protocols.\textsuperscript{41} Also, the origins of the assets are traceable (ie, the sources or the data and records can be confirmed),\textsuperscript{65} increasing the reusability of verified data (eg, for insurance transactions).\textsuperscript{70} Therefore, blockchain is suitable for use in managing critical digital assets (eg, patient consent records).

The fourth benefit is both robustness and availability. Although DDBMS and blockchain are based on distributed technology and thus do not suffer from single-point-of-failure, it would be costly for DDBMS to achieve the high level of data redundancy blockchain does (ie, each node has a whole copy of whole historical data records).\textsuperscript{64} Thus, blockchain is suitable when the preservation and continuous availability of records (eg, the electronic health records of patients) are important.

The final key benefit of blockchain is related to the improved security and privacy using cryptographic algorithms. For example, Bitcoin blockchain utilizes the 256-bit Secure Hash Algorithm (SHA-256), a cryptographic hash function defined in the US Federal Information Processing Standards 186-4, published by the National Institute of Standards and Technology,\textsuperscript{71} as the cryptographic hash function in the hash-chain that the proof-of-work algorithm runs on.\textsuperscript{72} SHA-256 is also used to generate user addresses for privacy/anonymity improvement (ie, each user is represented by a hash value instead of a real identity, such as an IP address).\textsuperscript{73} Furthermore, Bitcoin blockchain exploits the 256-bit Elliptic Curve Digital Signature Algorithm, an asymmetric cryptography algorithm defined in the US Federal Information Processing Standards 180-4,\textsuperscript{74} to generate and verify high-security-level public and private keys as digital signatures, and thus ensures ownership of the digital assets, as with patient records.\textsuperscript{74}

To summarize, the key benefits for adopting blockchain technology in biomedical and health care applications include: (1) decentralized management, (2) immutable audit trail, (3) data provenance, (4) robustness/availability, and (5) security/privacy.

**Figure 5. An example of how Bitcoin blockchain deals with branching chains.** In this scenario, attackers create malicious blocks ($M_1$ and $M_2$) to compete with an honest block ($H_2$), in an attempt to take over the honest chain ($H_1$ and all blocks before). Assuming the computational power of honest nodes is larger than that of malicious nodes, an honest block $H_2$ is created right after $H_2$, before the attackers create new malicious blocks after $M_1$ and $M_2$. Based on the blockchain mechanism, each node first identifies a valid block based on the length of the chain, and creates a new block ($N$) only at the end of the longest chain ($H_1$-$H_2$-$H_3$ in this example) while ignoring shorter chains ($H_1$-$M_1$ and $H_1$-$M_2$ in this example). In other words, the blockchain that has been worked on most wins the competition (ie, majority voting of “one CPU, one vote,”\textsuperscript{[1]} since the longest blockchain represents the majority decision of block creators). Given that the mining process is expensive and the honest nodes have higher computational power (ie, have more CPU “voters”) than the malicious nodes, the probability for the attacker to successfully modify a block and all blocks thereafter (ie, create a malicious competing chain) is very small.
**Table 1. Blockchain benefits and uses cases to improve medical record management**

| Blockchain: Key Benefit | Biomedical/Health Care Use Case: Improved Medical Record Management |
|-------------------------|---------------------------------------------------------------------|
| Decentralized Management | Patient-managed health care records: “[Patient] becomes the platform, owning and controlling access to their health care data. This removes all obstacles to patients acquiring copies of their health care records or transferring them to another health care provider.” |
| Immutable Audit Trail   | Unalterable patient records: “The data are stored in the private blockchain cloud. Blockchain may guarantee medical data cannot be changed by anybody including physicians and patients themselves/naturally.” |
| Data Provenance         | Source-verifiable medical records: “Records are signed by source, allowing legitimacy of records to be verified (and false records to be plausibly denied).” |
| Robustness/Availability | Reduced risk of patient recordkeeping: “Because data is stored on a decentralized network, there is no single institution that can be robbed or hacked to obtain a large number of patient records.” |
| Security/Privacy        | Increased safety of medical records: “Data is encrypted in the blockchain and can only be decrypted with the patient’s private key. Even if the network is infiltrated by a malicious party, there is no practical way to read patient data.” |

**Table 2. Blockchain benefits and use cases to enhance insurance claim process**

| Blockchain: Key Benefit | Biomedical/Health Care Use Case: Enhanced Insurance Claim Process |
|-------------------------|---------------------------------------------------------------------|
| Decentralized Management | Real-time claim processing: “The ability to remove intermediaries from a process is the capability that sets Blockchain apart from other technologies. This capability will allow the solution to facilitate real-time claim adjudication by replacing the health plan intermeditation with transparent Blockchain technologies.” |
| Immutable Audit Trail   | Improved claim auditing and fraud detection: “Payer, private and government insurers, and individual payers have the benefits of audit facilitation and better fraud detection [based on Blockchain immutability].” |
| Data Provenance         | Verifiable records for claim qualification: “[The chief obstacle of the claim qualification process] is the distributed nature of the many records that feed the decisions of patients, providers, and Medicaid administrators…The requirements for verification…are precisely the obstacles that a distributed blockchain solution…can address.” |
| Robustness/Availability | Enhanced accessibility of patient data: “[Provider, health-related services and medical goods have the benefits of] patient data accessible from multiple silos [based on Blockchain virtual ledger].” |
| Security/Privacy        | Increased security of patient medical insurance information: “[Member/patient have the benefits of] less likelihood of hacking of…financial information [based on Blockchain mechanisms].” |

**BLOCKCHAIN TECHNOLOGIES FOR BIOMEDICAL/HEALTH CARE APPLICATIONS**

As the benefits of blockchain described above are crucial for biomedical and health care applications, health care has become one of the most important emerging application areas of the blockchain distributed ledger technology. In general, blockchain is treated as the most important emerging application areas of the blockchain biomedical/health care applications, health care has become one of the most important emerging application areas of the blockchain biomedical/health care data ledger section. For each category of application, we further discuss the use cases and key benefits of adopting blockchain technology.

**Improved medical record management**

Many studies or ongoing projects focus on exchanging patient care data using blockchains to improve medical record management, including Healthcare Data Gateways, MedVault, Fatcom, BitHealth, Gem Health Network, and others. Several well-known companies, such as Deloitte and Accenture, are also involved in applying blockchain technology to store health care data and manage medical records. Another famous example is Guardtime, a company providing a blockchain-based system in Estonia to secure 1 million health records. The benefits and use cases of adopting blockchain to improve medical record management are summarized in Table 1.

**Enhanced insurance claim process**

Another important goal is to verify the claim transactions to support health care financing tasks (ie, health plan claims), such as preauthorization payment, alternative payment models, automatic claims using Fast Healthcare Interoperability Resources and smart contract, and Smart Health Profile to help manage the constant exit and reentry of Medicaid beneficiaries due to eligibility changes. The benefits and use cases of adopting blockchain to enhance insurance claim process are summarized in Table 2.

**Accelerated clinical/biomedical research**

Several researchers also propose accelerating secondary use of clinical data (ie, clinical and biomedical studies and research) using blockchain technology, including MedRec, Data Lake, Healthbank, and blockchain-based data sharing networks. Also, ModelChain adopted blockchain to increase the security and
robustness of the distributed privacy-preserving health care predictive modeling across multiple institutions. The benefits and use cases of adopting blockchain to accelerate clinical/biomedical research are summarized in Table 3.

### Advanced biomedical/health care data ledger

Besides exploiting blockchains as ledgers of patient care data (ie, HIE), many studies and projects have also proposed using them to store various types of health care–related data, such as genomic and precision medicine data, patient-centered or patient-related outcomes data, provider/patient directories and care plans data, clinical trial data, patient consent data, pharmaceutical supply chain data, and biomarker data. The benefits and use cases of adopting blockchain to accelerate clinical/biomedical research are summarized in Table 4.

### Table 3. Blockchain benefits and use cases to accelerate clinical/biomedical research

| Blockchain: Key Benefit | Biomedical/Health Care Use Case: Accelerated Clinical/Biomedical Research |
|-------------------------|--------------------------------------------------------------------------------|
| Decentralized Management | Improved care data sharing and analysis without ceding control: “Blockchain is by design a decentralized (ie, a peer-to-peer, non-intermediated) architecture. Each institution can keep full control of their own computational resources [while collaborating with other institutions for data sharing and analysis].” |
| Immutable Audit Trail | Trackable and timestamped patient-generated data: “Using Blockchain, this model could be even further individualized in a way that personal patient-generated health data which is available to researchers can be tracked in the research process with a timestamp.” |
| Data Provenance | Evidenced provenance for medical research data: “The MedRec [Blockchain-based prototype for electronic health records and medical research data] . . . enabled with crucial properties of provenance.” |
| Robustness/Availability | Superior health care data availability: “Blockchain would ensure continuous availability and access to real-time data. Real-time access to data would improve clinical care coordination and improve clinical care in emergency medical situations. Real-time data would also allow researchers and public health resources to rapidly detect, isolate and drive change for environmental conditions that impact public health. For example, epidemics could be detected earlier and contained.” |
| Security/Privacy | Secured and privacy-preserving health care data sharing: “Utilization of the . . . health blockchain . . . has the potential to engage millions of individuals, health care providers, health care entities and medical researchers to share vast amounts of genetic, diet, lifestyle, environmental and health data with guaranteed security and privacy protection.” |

### Table 4. Blockchain benefits and use cases to advance biomedical/health care data ledger

| Blockchain: Key Benefit | Biomedical/Health Care Use Case: Advanced Biomedical/Health Care Data Ledger |
|-------------------------|--------------------------------------------------------------------------------|
| Decentralized Management | Decentralized health data backbone: “The blockchain then becomes the backbone for digital health, incorporating data from patient-based technologies and the EMR to provide a . . . pool from which authorized users, such as providers and patients, has access. All of the data is stored in a decentralized manner, with no single entity storing or having singular authority to access.” |
| Immutable Audit Trail | Unchangeable log of clinical research protocols: “Use of blockchain technology has recently been shown to provide an immutable ledger of every step in a clinical research protocol, and this could easily be adapted to basic and experimental model science. All participants in the peer-to-peer research network have access to all of the time stamped, continuously updated data. It is essentially tamper proof since any change, such as to the prespecified data analysis, would have to be made in every computer (typically thousands) within the distributed network.” |
| Data Provenance | Ensure original manufacturer and ownership transferring in pharmaceutical supply chain: “Using Blockchain, the origin of the [medicine] product and its components are detected, and any transfer of ownership in each case is made clear and available to everyone. Forged, poor quality or stolen goods can be tracked and identified.” |
| Robustness/Availability | Improved robustness for counterfeit drug prevention/detection systems in pharmaceutical supply chain: “In the existing solutions, there is still a central authority that can be compromised and documents that can be faked . . . If [the current solutions] can be modified with blockchain-enabled anti-tampering capabilities during manufacturing, the supply and dispensation system could make drug counterfeiting a non-issue.” |
| Security/Privacy | Higher patient confidence in consent recording systems: “Patients are able to add consent statements at any point in their care journey – confident that the blockchain will hold them securely.” |

### POTENTIAL CHALLENGES AND PROPOSED SOLUTIONS FOR ADOPTING BLOCKCHAIN TECHNOLOGY FOR BIOMEDICAL/HEALTH CARE APPLICATIONS

Potential problems and challenges

There are several potential challenges to be considered when adopting blockchain technology in the biomedical/health care domain.
The first challenge is related to transparency and confidentiality. As “everyone can see everything” on a blockchain network, heightened transparency and decreased confidentiality, such as open transparency of information during transfer, is usually considered a limitation of blockchain. Also, even if a user is “anonymized” by using hash values as addresses, the user may still be reidentified through inspection and analysis of the publicly available transaction information on the blockchain network, and therefore the blockchain network only provides “pseudonymity.”

The second challenge is related to speed and scalability. The transaction time of blockchain can be long, depending on the protocol, and such a speed constraint may limit the scalability of blockchain-based applications. For example, with the proof-of-work protocol, there are about 288,000 transactions per day (or about 3.3 transactions per second) on average for Bitcoin due to the required computation workload, while there are 150 million transactions per day (or about 2000 transactions per second) on average for a credit card like Visa.

The threat of a 51% attack on the biomedical/health care blockchain network may suffer from the “51% attack,” which happens when there are fewer honest nodes than malicious ones in the whole network, and thus the whole network is taken over by the malicious attackers (Figure 6). This issue is also critical for security-demanding health care/biomedical applications.

### Proposed solutions and implementations

The above challenges can be mitigated by careful design and implementation of the biomedical/health care application systems. We take ModelChain as an example. ModelChain adopts blockchain to securely and robustly disseminate privacy-preserving predictive models (ie, a set of machine learning parameters or aggregated values) between health care institutions. Because it only disseminates predictive models but not PHI, transparency is not a critical issue. Also, it contains a machine learning process that can take a long time to run (minutes, or even hours), thus the transaction speed of blockchain becomes relatively negligible. Finally, since it adopts permissioned blockchain networks, malicious nodes could not arbitrarily participate in the network, and therefore the risk of a 51% attack is minimal.

Other implementation techniques to mitigate the transparency confidentiality issue include encrypting sensitive data (eg, PHI or personal identifiable information) on the blockchain network, storing sensitive data off-blockchain and only disseminating “pointers” (eg, encrypted links) or permission information on-blockchain, and automating data management protocols using smart contracts.

To deal with the speed/scalability issue, plausible solutions include exploiting blockchain as an index of health data instead of the repository of all records, and storing only ongoing verified transactions rather than the complete history on blockchain. Also, several new blockchain implementations, such as BighainDB, provide significantly higher transaction speed than the Bitcoin blockchain, which could also solve the speed and scalability problem.

### CONCLUSION

We introduced Bitcoin and the underlying blockchain technology, which provides decentralized management, an immutable audit trail, data provenance, robustness/availability, and security/privacy. We contrasted blockchain technologies (ie, blockchain 1.0, 2.0, and 3.0), identified benefits of blockchain compared to traditional distributed databases for biomedical/health care applications, and provided an overview of the latest biomedical/health care applications of blockchain.

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**Figure 6.** An example of 51% attack. In this scenario, attackers create malicious blocks (M1 and M2) to compete with an honest block (H2), trying to take over the honest chain (H1 and all blocks before). However, this time the computational power of host nodes is smaller than that of malicious nodes (ie, malicious nodes control more than 51% of the computing power on the network), thus a malicious block M3 is created right after M2. Based on the blockchain mechanism, the new block (M3) will be created only at the end of the longest chain (H1→M2→M3 in this example). Therefore, the attacker has successfully modified the blockchain record (from H2 to M2) and takes over the chain by winning the majority vote.
technology (ie, improved medical record management, enhanced insurance claim process, accelerated clinical/biomedical research, and advanced biomedical/health care data ledger). There are several known potential challenges to adopting blockchain technologies (eg, transparency/confidentiality, speed/scalability, and the threat of a 51% attack). However, these challenges can be addressed through careful application design and implementation, therefore health care applications of blockchain continue to increase. Blockchain distributed ledger technology can advance the biomedical and health care domains in various novel ways, and we expect many new applications to emerge soon.

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**COMPETING INTERESTS**

The authors have no competing interests to declare.

**CONTRIBUTORS**

T-TK conducted the literature review and drafted the manuscript. HK added critical discussion points and edited the manuscript. LO-M was principal investigator of this study; she provided the original idea, overall supervision of this study, and critical editing of the manuscript.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at Journal of the American Medical Informatics Association online.

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