**Electronic medical record**

Chapter I EMR construction 2

eMERGE Phase I 2

EMR Phase II [eMERGE-II] 2

eMERGE Application case—balanced crystalloids and Saline 3

Geisnger 3

GERA 3

Partners Healthcare System 4

自然语言处理 4

工具cTAKES 4

诊断实例 4

Chapter 2 AI 5

视网膜应用 5

Google Brain AI 5

DeepMind 6

TensorFlow代码 6

# Chapter I EMR construction

EMR连接的是病人，医生，以及医疗系统本身。

### eMERGE Phase I

The Electronic medical record and genomics (eMERGE) network review1

**NHGRI, March 2007, Phase I [eMERGE-I]-Vanderbilt University**

Five sites:

“In September 2007, grants were awarded to five sites (hereaf- ter referred to as eMERGE-I)—Group Health Cooperative/University of Washington, Marshfield Clinic, Mayo Clinic, Northwestern University, and **Vanderbilt University**, which also served as the network’s **coordinating center**.”  
eMERGE-II (9 sites):

CHOP [Children’s hospital of Philadelphia], GHC & U Wash, Mount Sinai, CCHMC & BCH [Cincinnati Children’s Hospital Medical Center with Boston Children’s Hospital], Marshfield & Essentia, Northwestern, Geiginger, Mayo, Vanderbilt

Three major aims:

1 EMR for robust electronic phenotyping;

2 conduct GWAS using the phenotypes derived in the above-mentioned first aim; PheGWAS2

3 explore the ethical, legal, and social implications associated with EMR-based GWAS and wide-scale data sharing.

The workgroups included:  
an informatics group [published a phenotyping algorithm, PheKb: Phenotype KnowledgeBase, 20http://www.PheKb.org]. Developed by the first site and deployed to the second, and then across the network.   
a genomics group [imputation, strand issue, relatedness, ],   
and a consent and community consultation group [model language for EMR-linked ].

**Lesson learned from Phase I**

1 Phenotyping across the network rather than local sites.

2 Most eMERGE Participants have consented to contributing their data to health research of any kind. Through network-wide projects, eMERGE-I was compelled to develop best practices for sharing genomic data and EMR-derived phenotypes while protecting the privacy of participants.

3 Returing of results (RoR) 3. Turner syndrome, Klinefelter syndrome, FVL, hereditary hemochromatosis. There is no clear agreement how the finding should be returned. In some case, the clinically actionable results identified in EMR was already known. “In some case, health records shed light on ambiguous findings, increasing the likelihood that some findings represented acquired rather than congenital genetic changes.”

### EMR Phase II [eMERGE-II]

Phenotyping workgroup

Genomics workgroup

RoR workgroup

Consent, education, regulation, and consultation workgroup: evaluating the impact of returning hemochromatosis results

EMR integration workgroup: PGx [pharmcogenomic] pilot project

Collaboration with external groups

**Lessons**

1 Portability of electronic phenotypes within and outside eMERGE

“There is currently no formal phenotyping language for the purpose of building EMR phenotyping algorithms nor is their a common approach to their implementation.

2 Approaches to EMR integration of genomic information

3 Integration of pediatric sites

4 Longitudinal cost-effective genomic medicine discovery and implementation

5 Generalized framework for the return of genomic results

6 The eMERGE network in the context of a translational framework.   
T0: early phases focusing of biologic discoveries (eMERGE-I focused large on T0)  
T1: development of candidate health applications (eMERGE-II)

T2: assessing outcomes of intervertions

T3: move genomic findings into health practice.

T4: public health surveillance

### eMERGE Application case—balanced crystalloids and Saline

Balanced crystalloids与生理盐水Saline一直在临床使用上有争议，但差异可能比较小，而要组织能够区分这类差异的临床试验比较困难。之前两者的差异一直基于生理角度分析，而EMR的出现，让大规模基于病人的循证医学成为一个选项。

**Case 1:** Balanced crystalloids versus saline in the intensive care unit: The SALT randomized trial4. Data 2015/Feb/3~2015/May/31

**Case 2:** Balanced Crystalloids versus Saline in critically Ill Adults5. 2015/Jun/1~2017/4/30.

In particular, the design and the protocol of the study was published in BMC Trials6. Screenplay -> movie.

在这个Vanderbilt基于eMERGE之前的标杆研究是新西兰多中心的SPLIT RCT研究7—收集了1000：1000的buffered crystalloid 和 saline，当没有显示差异。

Vanderbilt的这个研究展示了一个比较完整的pre-study，design，到大规模实验的流程。

在prestudy中4，使用了2015/Feb/3-2015/May/31的数据，454saline，520 balanced crystalloids。也就是说，仅仅基于Vanderbilt ICD三个月的EMR数据量就赶上了新西兰的研究水平。

实验设计的具体流程则在Trials上发表6，最终发表了基于2015/jun~2017/April的数据，样本量达到15802(7942 balanced-crystalloids group, 7860 saline group)，也就是case 2。

**Case 3:** Balanced crystalloid versus saline in noncritically ill adults8.

## Geisnger

Geisinger9 [The Geisinger MyCode community health initiative: an electronic health record-linked biobank for precision medicine research]

1996 started to collect EMR

2007 GHS launched a project now known as MyCode Community Health Initiative to create a system-wide biorepository of blood serum and DNA samples for broad research used, including genomic analysis.

In their demo, the loss-of-function *APOC3* was tested. *APOC3* had strong effect in lipd values10

## GERA

**GERA [Genetic Epidemiology Research on Adult Health and Aging cohort]**11

About a cohort of > 100,000 subjects who are participants in the Kaiser Permanente Medical Care Plan, Northern California Region. 20% African Africa, Asian, and Latino or mixed, 80% non-Hispanic white.

Affymetrix Axiom Genotyping chip designed by GERA12,13.

Saliva-based genotyping experiments, Oragene OG-250 disc format saliva kit.

Population genetics study analysis for GERA found about 3400 Chinese samples14.

GERA also measure Telomere Length15. It was pretty petty because mDNA provided a much accurate measure for aging compared with Telomere length16.

## Partners Healthcare System

**Partners Healthcare System (**<https://www.partners.org/About/Default.aspx>**)**

**Founding members**

Brigham and Women’s Hospital, Massachusetts General Hospital

International code of disease [<https://www.who.int/classifications/icd/en/>]

Natural Language Processing and EMR

Open source NLP cTAKES <http://ctakes.apache.org/>

Unified Medical Language System (UMLs)17 <https://www.nlm.nih.gov/research/umls/knowledge_sources/metathesaurus/>

Compared with using ICD code in billing data alone for treatment resistant depression as a model18.

Using NLP in EMR to identify pregnant women with suicidal behavior: towards a solution to the complex classification problem19.

## 自然语言处理

### 工具cTAKES

基于physicians’s notes and radiology reports offers a valuable resource for defining clinical phenolypes.

Zhong就报告了一个用cTAKES[<http://ctakes.apache.org/>]技术提取医师记录19,20

“Based on the Unstructured Information Management Architecture (UIMA), cTAKES is a comprehensive clinical NLP tool that processes clinical notes and identifies terms. cTAKES maps the terms to a subset of the Unified Medical Language System (UMLS) Metathesaurus the Systemized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) [42], and assigns each term a UMLS con- cept unique identifier (CUI)”20

### 诊断实例

以Partners Healthcare System的数据为例20，诊断孕妇是否有自杀倾向，虽然可以提高sensitivity，但有很高的假阳性，只有30%用NLP发现的case通过人工审查确认是真实的20。这也是NLP处理数据时候面临的问题，比如

“In the Partners HealthCare EMRs, we observed a major negation structure for suicidal behavior: terms related to suicidal behavior were followed by a colon and a negation word without any sentence punctuation (e.g., “suicidal behavior: none,” “suicidal behavior: none reported,” and “suicidal behavior: denied”)”20

# Chapter 2 AI

AI是机器学习的一个子类，近几年表现优异，在图像识别，语言处理，对话中都有进展。

ML从根本要求上，是能够从输入数据，达到所需要的输出结果。Deep learning则是一种表示学习（representation learning），并且能够自动设计layer，从raw data一直到最后的分类。

Reinforcement learning (RL)则可以从专家演示从学习

## 视网膜应用

Nature Medicine 2019 January has an issue for Medicine in Digital Age, 其中包括Stanford与google的Deep learning 论文21，FDA也已经批准这个软件的使用22。

以及广州中山医科大学与UCSD合作的论文23。

在“A guide to deep learning in healthcare”中21，Jeff Dean和成员主要描述了AI在医学中，特别图像识别中的一系列应用，其中convolutional neural networks (CNNs)

由USCD张康领衔的团队，运用TensorFlow技术训练的眼科技术，2018年2月发表在cell上24，目前已经被用于喀什第一人民医院的眼科诊断[<http://www.jinciwei.cn/k212206.html>

]，因为此地区眼疾发病比较高，包括diabetic retinopathy，glaucoma，retinal vein occlusions和age-related macular degeneration (见其cell论文)。

AI技术目前来看最有可能使用的是图像密集型的医学领域，比如radiology，pathology，ophahalmology，和dermatology25[注，这个例子似乎石瑜提到过，有些over-fitting的问题]。这是因为目前AI在图像识别领域是做的最好的。

组织的显微分析

Google Brain基于AI技术实现了组织的显微分析，AUC达到90%以上26。

A comment about three pitfalls to avoid in machine learning27。

Data sharing

Transparency

1 监督算法的要求

2 模型可解释性的要求 <https://christophm.github.io/interpretable-ml-book/>

3 算法的可能偏向性

Patient safety

## Google Brain AI

A very popular example is Google Brain AI using deep learning28 (using two public data EyePAC-1 and Messidor-2) to screen for diabetic retinopathy29[India Aravind eye hospital, india], and for multiethnicities populations with diabetes30 (see their table 1 for population setup).

“the DLS consisted of a convolutional neural network to implicitly recognize characteristics of preferable diabetic retinopathy, possible glaucoma, and AMD from the appearance in retinal images.”

“the primary analysis was to determine if the DLS was equivalent or better than 2 trained senior nonmedical professional graers (>5 years’ experience) currently employed in the SIDRP in detecting referable diabetic retinopathy and vision-threatening diabetic retinopathy, with reference to a retinal specialist (>5 years experience in diabetic retinopathy grading).”

Camera: Topcon, FundusVue, Canon, Carl Zeiss

Tank problem (Kadanl, LN & Randall, NC, 1964, 19th ACM National Conf)

Common problems with AI

1 Splitting data inappropriately: the received data is different from the real world

2 Hidden variable (tank is detected because of clouds there)

3 Mistaking the objective (loss function is nonsense)

## DeepMind

**Summary： DeepMind用Deep Learning技术对来自美国老兵医疗系统的数据进行挖掘，可以预测急性肾损伤（Acute Kidney Injury)** 31**。此论文的Ref 2-17引用了一些列相关的机器学习算法。**

**背景：在美国AKI affects approximately one in five inpatient admission in US。**

**传统方法：传统使用的是serum creatinine as a marker of acute decline in renal function。**

**数据训练：使用了703,782个来自美国老兵医院(US Department of Veterans Affairs)的EMR记录。**

**“Patients were randomized across training (80%), validation (5%), calibration (5%) and test (10%) sets.  
数据标签：A ground-truth label for the presence of AKI at any given point in time was added using the internationally accepted ‘Kidney Disease: Improving Global Outcomes’ (KDIGO) criteria18; the incidence of KDIGO AKI was 13.4% of admissions.”**

### TensorFlow代码

**基于TensorFlow，论文还在github上提供了代码**

**“We make use of several open-source libraries to conduct our experiments: the machine learning framework TensorFlow (https://github.com/tensorflow/tensor- flow) along with the TensorFlow library Sonnet (https://github.com/deepmind/ sonnet), which provides implementations of individual model components”**

## AI的问题

**为什么Deep Learning is so easy to fool**32**. “**No one really has any idea how to better it,” says Clune

**由于AI可能的滥用，已经开始“Montreal Declearation”[[1]](#footnote-1)**

**Reference**

1. Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genet. Med.* **15**, 761–71 (2013).

2. Denny, J. C. *et al.* PheWAS: Demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics* **26**, 1205–1210 (2010).

3. Fullerton, S. M. *et al.* Return of individual research results from genome-wide association studies: Experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genet. Med.* **14**, 424–431 (2012).

4. Semler, M. W. *et al.* Balanced crystalloids versus saline in the intensive care unit: The SALT randomized trial. *Am. J. Respir. Crit. Care Med.* **195**, 1362–1372 (2017).

5. Semler, M. W. *et al.* Balanced Crystalloids versus Saline in Critically Ill Adults. *N. Engl. J. Med.* **378**, 819–828 (2018).

6. Semler, M. W. *et al.* Balanced crystalloids versus saline in the intensive care unit: Study protocol for a cluster-randomized, multiple-crossover trial. *Trials* **18**, 129 (2017).

7. Young, P. *et al.* Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: The SPLIT randomized clinical trial. *JAMA* **314**, 1701–1710 (2015).

8. Self, W. H. *et al.* Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N. Engl. J. Med.* **378**, 819–28 (2018).

9. Carey, D. J. *et al.* The Geisinger MyCode community health initiative: An electronic health record-linked biobank for precision medicine research. *Genet. Med.* **18**, 906–913 (2016).

10. The TG and HDL Working Group of the Exome Sequencing Project. Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. *N. Engl. J. Med.* **371**, 22–31 (2014).

11. Kvale, M. N. *et al.* Genotyping Informatics and Quality Control for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics* **200**, 1051–1060 (2015).

12. Hoffmann, T. J. *et al.* Next generation genome-wide association tool: Design and coverage of a high-throughput European-optimized SNP array. *Genomics* **98**, 79–89 (2011).

13. Hoffmann, T. J. *et al.* Design and coverage of high throughput genotyping arrays optimized for individuals of East Asian, African American, and Latino race/ethnicity using imputation and a novel hybrid SNP selection algorithm. *Genomics* **98**, 422–430 (2011).

14. Banda, Y. *et al.* Characterizing Race/Ethnicity and Genetic Ancestry for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics* **200**, 1285–1295 (2015).

15. Lapham, K. *et al.* Automated Assay of Telomere Length Measurement and Informatics for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics* **200**, 1061–1072 (2015).

16. Horvath, S. DNA methylation age of human tissues and cell types. *Genome Biol.* **14**, R115 (2013).

17. Bodenreider, O. The Unified Medical Language System (UMLS): Integrating biomedical terminology. *Nucleic Acids Res.* **32**, 267–270 (2004).

18. Perlis, R. H. *et al.* Using electronic medical records to enable large-scale studies in psychiatry: Treatment resistant depression as a model. *Psychol. Med.* **42**, 41–50 (2012).

19. Zhong, Q.-Y. *et al.* Use of natural language processing in electronic medical records to identify pregnant women with suicidal behavior: towards a solution to the complex classification problem. *Eur. J. Epidemiol.* **34**, 153–162 (2019).

20. Qiu-Yue, Z. *et al.* Screening pregnant women for suicidal behavior in electronic medical records: diagnostic codes vs. clinical notes processed by natural language processing. *BMC Med. Inform. Decis. Mak.* **18**, 30 (2018).

21. Esteva, A. *et al.* A guide to deep learning in healthcare. *Nat. Med.* **25**, 24–29 (2019).

22. Nature Medicine. Medicine in the digital age. *Nat. Med.* **25**, 1 (2019).

23. He, J. *et al.* The practical implementation of artificial intelligence technologies in medicine. *Nat. Med.* **25**, 30–36 (2019).

24. Kermany, D. S. *et al.* Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell* **172**, 1122-1131.e9 (2018).

25. Esteva, A. *et al.* Dermatologist-level classification of skin cancer with deep neural networks. *Nature* **542**, 115–118 (2017).

26. Chen, P.-H. C. *et al.* An augmented reality microscope with real-time artificial intelligence integration for cancer diagnosis. *Nat. Med.* (2019). doi:10.1038/s41591-019-0539-7

27. Riley, P. Three pitfalls to avoid in machine learning. *Nature* **572**, 27–29 (2019).

28. LeCun, Y., Bengio, Y. & Hinton, G. Deep learning. *Nature* **521**, 436–444 (2015).

29. Gulshan, V. *et al.* Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA* **316**, 2402–2410 (2016).

30. Ting, D. S. W. *et al.* Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA* **318**, 2211–2223 (2017).

31. Tomašev, N. *et al.* A clinically applicable approach to continuous prediction of future acute kidney injury. *Nature* **572**, 116–119 (2019).

32. Heaven, D. Why deep-learning is so easy to fool. *Nature* **574**, 163–6 (2019).

1. <https://mila.quebec/en/2018/12/official-launch-of-the-montreal-declaration-for-responsible-development-of-artificial-intelligence/> [↑](#footnote-ref-1)