Panel 2:
Safety and Efficacy Concerns for Ophthalmic Digital Devices in Differing Use Settings

The Ophthalmic Office
Non Eye-Care Clinical Environments
Non Clinical Environments Including the Home and Workplace

Panel 2
Safety and Efficacy In and Out of the Office

Moderators:
  Ken Nischal University of Pittsburgh
  Mark Blumenkranz Stanford University

Panelists:
  Michael Abramoff University of Iowa
  Zach Bodnar Stanford University
  Michael Chiang Oregon Health Sciences University
  Michael Goldbaum UCSD
  Quinton Oswald Notal Vision
  Linda Zangwill UCSD
Digital Health Provides Value Propositions To All Stakeholders In Healthcare System

- Reduced costs
- Improved outcomes
- Data-based insights
- Value-based analysis
- Improved workflow
- Expanded reach
- Patient engagement
- Increased engagement
- Better care
- Improved convenience
- Reduced costs
- Improved outcomes

Patients

Physicians

Pharma

Payers


Ageing Of 50-64 Demographic Driving Rapid Increase Of Smartphone Utilization In Senior Population

Smartphone Usage by Americans 65+ Years of Age

<table>
<thead>
<tr>
<th>Year</th>
<th># of Americans 65+ Years of Age</th>
<th>% of Americans 65+ Years of Age</th>
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<tbody>
<tr>
<td>2012</td>
<td>4.5</td>
<td>10%</td>
</tr>
<tr>
<td>2013</td>
<td>7.6</td>
<td>15%</td>
</tr>
<tr>
<td>2014</td>
<td>12.3</td>
<td>20%</td>
</tr>
<tr>
<td>2015</td>
<td>16.2</td>
<td>25%</td>
</tr>
<tr>
<td>2016</td>
<td>20.0</td>
<td>30%</td>
</tr>
</tbody>
</table>

Smartphone Capabilities Are Orders Of Magnitude Greater Than Legacy Computing Systems

1984

72 dpi resolution
96,000 px camera
6 MHz speed
1 Mb storage

2005

326 dpi resolution
8,001,700 px camera
1.4 GHz speed
64 Gb storage

(4.5x) (83x) (233x) (64,000x)


Smart Devices Are Capable Of Diagnostic/Test Functions And Can Be Seen Across Healthcare

ASTHMA
CARDIOVASCULAR
ENT
ONCOLOGY
DIABETES
### Mobile / Portable Technologies In Eyecare

<table>
<thead>
<tr>
<th>Home Use</th>
<th>Clinician Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision Testing</td>
<td>Refractive Testing</td>
</tr>
</tbody>
</table>

- **DIGISIGHT TECHNOLOGIES**
- **OPTERNATIVE**
- **.peek**
- **icare**
- **EYENETRA**
- **WelchAllyn**
- **BioFormatix**
- **Vital Art and Science**
- **EyePhotoDoc**
- **gobiquity**
- **Smart Vision Labs**
- **OphthalmicDocs**
- **D·EYE**
- **PLEN'OPTIKA**
- **DIGISIGHT TECHNOLOGIES**
- **JEDMED**

---

**A Number of Portable Smartphone Based Photographic Systems Are Now Commercially Available**

- **DIGISIGHT TECHNOLOGIES**
- **VITAL ART AND SCIENCE**
- **WELCH ALLYN**
- **PEEK**
The FDA Has Cleared More Than 100 Mobile Health Apps For Medical Use

U.S. mHealth Market Size Is Expected To Grow By More Than 6x Between 2015 And 2020

SOURCE: Adapted from Grandview Research, “mHealth Market Analysis By Service, By Participants And Segment Forecasts To 2020,” August 2015.
Safety and Effectiveness Specifics

• What are the important safety and effectiveness concerns for an ophthalmic digital health device for the screening or monitoring progression of

  • *Macular Disease*

  • *Glaucoma*

In an Eye Care Clinical Environment

• Who if anyone needs to be specifically trained in the office to ensure efficiencies of workflow and the accuracy reproducibility and safety of the testing

• Do specific roles need to be developed to facilitate that process

• Should we now be tackling the question of specific reimbursement for testing with digital tools in the office versus outside the home
What about in other Clinical Environments  
Such as Primary Care or the ER

• What experience do we have now for interfacing between eye healthcare professionals and primary and urgent care providers

• What lessons can we draw from those experiences

What about Non-Clinical Environments  
Such as the Workplace or Home

• Is symptom diagnosis and triage analysis safely left to the potential patient

• Are there digital pharma innovations that could be applied in these circumstances such as tailoring of return visits or modifying treatments
Artificial Intelligence (AI)

• How will (AI) Affect the Use of Ophthalmic Digital Tools in the Future
• Are there Specific AI examples that help us negotiate these issues now, eg Interpretation of fundus photos for retinal disease screening

AI Enabled Image Analysis Questions

• Are we ready for fully automated interpretation?
• Does the AI/DL algorithm give the patient or doctor a diagnosis and/or plan?
• Or….Does the patient’s MD make the reading enabled by the AI?
• Or….Does a third party doctor read the results?
Correlations to Current Testing

• How closely do the results from in office or out of office testing have to correlate with traditional non digital measures to be effectively used in clinical practice
• How much training is required for patients in office and in home to insure reasonable accuracy and reproducibility

Safety and Privacy Concerns

• How do we these concerns regarding the storage of information on personal devices in the era of common cloud backup for other data on personal phones for technicians and patients
• How does monitoring of patient behavior and location relate to safety and efficacy concerns
Patient-activated, Cloud-based Platform: 3 Million Tests Complete, Personalized Monitoring System

Data automatically sent
Compliance reminders
Schedule visit
NOA-generated pre-specified alerts

PHYSICIAN

Using AI to Automate Analysis of Home-based OCT Output

IDENTIFIES FLUID/ LESION ACTIVITY

NOA RANK:

1 2

B-Scan No.: 65 37

SCORES AND RANKS LEVEL OF LESION ACTIVITY

NOA Rank: 1 2 3 4 5 6 7 8 9 10

RELIABLE AND ACCURATE

Source: N=142 Eye Study

NOA vs majority of 3 Retina Specialists
Individual Reader vs majority of 3 Retina Specialists

THE NOTAL OCT ANALYZER (NOA)

94% 92% 91%
94% 92% 91%
General Observations on Frequent Home Testing Data

• Much easier to track changes with **graphic** rather than traditional tabular output
• There is a short learning curve for the first several measurements but in **normal** eyes measurements are typically very consistent after 2-3 tests
• In **affected** eyes there tends to be intraday and day to day variability and data spread/noise possibly related either to diurnal variation and gravitational influences affecting macular fluid volume and/or variable response to photo-bleaching secondary to disease
Why Healthcare Needs Automation

![Graph showing US Labor Productivity from 1950 to 2010.](https://data.bls.gov/pdq/SurveyOutputServlet)

Electronic Patient Records lower physician productivity

**Electronic health record impact on productivity in an academic pediatric ophthalmology practice**

Travis K. Reid, BS,1 Sarah Broid-Brown, BA,1 Dongseok Choi, PhD,2,3 Thom D. Daniel C. Tsu, MD PhD,2,3 and Michael F. Chiang, MD2,4

**Purposes**

To measure the effect of electronic health record (EHR) implementation and efficiency in the pediatric ophthalmology division at an academic medical center.

**Methods**

Four established providers were selected from the pediatric ophthalmology division at Oregon Health & Science University. Charts were reviewed before and after EHR implementation. Time spent from completion of ophthalmic examination to chart completion was monitored for 3 years following implementation.

**Results**

Overall there was an 11% decrease in clinical work following EHR implementation, which was not statistically significant (P = 0.18). The mean OTC time was 26.5 hours among providers in the study, and trends over time were the same regardless of time spent, as there was no difference in productivity.

**Conclusions**

EHR implementation was associated with a negative impact on productivity in our pediatric ophthalmology division. (J AAPOS 2014;18:584-589)
Setting up AI based DR interpretation in four hours

<table>
<thead>
<tr>
<th>Hrs.</th>
<th>Personnel</th>
<th>Qty</th>
<th>Personnel Req.</th>
<th>Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>Technician</td>
<td>1</td>
<td>None</td>
<td>Site Setup Checklist</td>
</tr>
<tr>
<td>4.0</td>
<td>Trainer</td>
<td>1</td>
<td>IDx Cert.</td>
<td>Operator Training Manual</td>
</tr>
<tr>
<td></td>
<td>Operator</td>
<td>2-3</td>
<td>High School Degree</td>
<td>Training PowerPoint Presentation</td>
</tr>
<tr>
<td></td>
<td>Volunteer Subjects</td>
<td>10</td>
<td>Consent</td>
<td>Training Photography Consent Form</td>
</tr>
</tbody>
</table>

Reimbursement

• AI in Ophthalmology enormous potential to increase efficiency

• enormous dependence of the business model / ROI on reimbursement

• If there is a path for reimbursement, investment will follow. If path is iffy, investment much riskier.

• All Medicare reimbursement is clinician-workload derived.

• AI diagnostics have just never been on the radar
AI indications for use

Discussing with FDA the following use case items

- Autonomous use including in primary care
- Used by non eye-care providers
- Specific levels of diabetic retinopathy
- For subjects who have not been previously diagnosed with diabetic retinopathy.
Interfacing: Interpretation issues

• Current DR screening rates ~10-30%
• Autonomous interpretation will lead to giant increase in (retinal) diagnostics
  – non eye-care professionals
  – emphasis on primary care
• Here, comfort with ICDR, let alone ETDRS, outputs is low
  – Align outputs with PPPs and other standards

Align outputs with PPP

<table>
<thead>
<tr>
<th>AI system Output</th>
<th>AAO PPP Disease Level</th>
<th>Progression to High Risk PDR (1 Year)</th>
<th>Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Mild DR</td>
<td>Normal or Minimal NPDR Mild NPDR</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>mtmDR</td>
<td>Moderate NPDR</td>
<td>1.2% - 8.1%</td>
<td>Commonly</td>
</tr>
<tr>
<td>vtDR</td>
<td>Severe NPDR</td>
<td>17.1%</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Interfacing: Hand-off issues

- If AI identifies need for eye-care referral
  - Can I get patient in
  - Did patient get examined / treated and what was outcome
- Continuity of care report or similar way to track path of patient through system

Shift from Eyecare Diagnostics to Non-Eyecare AI
AI Algorithm design

Lesion-Based AI Disease Detection

Quality Assessment

Pass

Anatomy Localization

Disease Assessment

Straight CNN Disease Detection

Disease Assessment

Straight CNN algorithms susceptible to catastrophic failure:
Lesion based algorithms are robust

Lynch et al, ARVO 2017; submitted, PLOS One
ATA Guidelines for Systems for Automated and Computer Assisted Detection, Staging and Diagnosis of DR

Level | Autonomy Level description | Specialist Physician Actions | Disease aware | Example
--- | --- | --- | --- | ---
1 | No automation | Viewing | - | Any photoviewer
2 | Viewing with non-disease specific tools | Viewing measuring | - | ImageJ[17], Photoshop[18]
3 | Computer assisted lesion/abnormality enhancement | Viewing Disease specific enhancement | yes | Intelligent PACS with lesion enhancement
4 | Automated detection / staging with expert readover of subset | Viewing All of the above | yes | Research prototype systems only (US)
5 | Automated detection / staging / diagnosis | No viewing | yes | Research prototype systems only (US)

1. Introduction

Automated and computer assisted detection, staging, and diagnosis of diabetic retinopathy (DR) can potentially improve clinical efficiency and accuracy. Guidelines for implementation can contribute to clinical introduction and quality of care. Thoughtful introduction of AI is especially important, because productivity in healthcare has been lagging behind that in other sectors, and may in fact be declining.[1]

Low productivity and the resulting high cost lead to lack of accessibility and affordability, partially caused by inappropriate introduction of information technology.[2-5] Automated medical diagnosis, a pre-requisite to improve health care efficiency, affordability, and accessibility[6], is a subject of great interest. Diagnostic algorithms have now achieved parity or even superiority to clinical experts for an increasing number of clinical tasks that use images as input, including diabetic retinopathy detection.[7]

In addition to their potential to improve productivity, diagnostic algorithms that base their output on the analysis of medical images eliminate the diagnostic variability that is common in expert review of medical images. [8-14] Such algorithms also have the potential to reduce or eliminate healthcare disparities due to geographic and socioeconomic barriers by increasing accessibility and affordability.

The American Diabetes Association has estimated that 30.3 million Americans, or 9.4% of the population, have diabetes,[15] and diabetes is still the primary cause of visual loss and blindness in the working age population. Approximately 25,000 people lose vision every year because of diabetic retinopathy (DR). Advances in image processing and computer vision have the potential to change the future of this disease.
Pipeline: Humphrey 24-2 perimetry from OCT

Early

Moderate

Severe

Bogunovic, IOVS 2015
Guo, IOVS 2017

Panel 2 Discussion

Michael F. Chiang, MD
Knowles Professor of Ophthalmology & Medical Informatics and Clinical Epidemiology
Vice-Chair (Research), Department of Ophthalmology
Casey Eye Institute at Oregon Health & Science University
National Vision for Quality Improvement

- NAM (2012): Best Care at Lower Cost
  - “Continuously learning health care system”: developing knowledge, translating new information into medical evidence, applying new evidence to patient care
  - Role of big data, registries, expert systems
  - FDA: expert systems can learn from feedback, benefits of flexibility in maintenance of approval

Telehealth Evolution

- Telemedicine: different patient-doctor interaction → better delivery?
- Remote screening: improved accessibility → wider net? Who interprets?
- Remote monitoring: more frequent visits → better outcomes? Who interprets?
In the Eye Care Environment

• Who captures the data?
  – Potential role for certification: not a new problem (e.g. certification of photographers for new ophthalmic imaging devices)

• Who interprets the data to make diagnostic & management decisions? Potential safety & variability issues:
  – If done by managing ophthalmologist: same patient-doctor relationship, not a new problem (e.g. lab tests, ABO, credentialing)
  – If done by remote reading center with “doctor” or “trained readers”: potential FDA issue for system (different patient-doctor relationship) & reader certification & delegation of responsibilities [especially if in non-eye care clinical environment or patient homes]
  – If done automatically by system: FDA issue for system
  – Who is liable from medicolegal perspective?

Outside the Eye Care Environment

• How is the diagnosis made?
  – If done by remote reading center with “doctor” or “trained reader”: potential FDA issue for system (no patient-doctor relationship) & reader certification & delegation of responsibilities
  – If done automatically by system: FDA issue for system

• If system is for non-eye clinical environment:
  – Who is responsible for collecting data? Potential certification issues
  – Who is responsible for interpreting & following-up on data? Above issues, plus reimbursement questions

• If system is for non-clinical environment → data overload:
  – Managed by patients? Not a new problem (e.g. home BP cuff)
  – Automated monitoring? New problems...
### Outside Office: Remote Monitoring

<table>
<thead>
<tr>
<th>MRN</th>
<th>Name</th>
<th>DOB</th>
<th>Sex</th>
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</thead>
<tbody>
<tr>
<td>3386531</td>
<td>GAGE, LINDA</td>
<td>1947-04-19</td>
<td>M</td>
</tr>
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<td>4141414</td>
<td>JOYCE, JAMES</td>
<td>1949-01-01</td>
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<tr>
<td>8888888</td>
<td>MOORE, DEMO</td>
<td>1980-01-15</td>
<td>F</td>
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<tr>
<td>3131313</td>
<td>SANDIEGO, CARMEN</td>
<td>1951-05-26</td>
<td>M</td>
</tr>
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<td>2121212</td>
<td>STAR, TREK</td>
<td>1966-09-01</td>
<td>F</td>
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<td>3937549</td>
<td>STRANGE, BOB</td>
<td>2000-02-02</td>
<td>M</td>
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<tr>
<td>3937494</td>
<td>MOON, DOGGIE</td>
<td>1001-01-01</td>
<td>M</td>
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<td>3937494</td>
<td>MOON, DOGGIE</td>
<td>1001-01-01</td>
<td>M</td>
</tr>
</tbody>
</table>

### Remote Monitoring Challenge

![Graph showing human effort against filtering ratio](image)

Tolerance Threshold?

Justin Starren, MD, PhD
Outside Eye Setting: Data Concerns

- Data accuracy
  - Analogy to patient-entered questionnaires
  - Who captured it? Level of trust?
  - Implications for EHRs and registries: importance of identifying source ("garbage in, garbage out", IRIS Registry experience)

- Who will review it from the health care team (if anyone)?
  - Training, reimbursement, can it be patients themselves

- Who will perform the diagnosis and management?

- Where is the medicolegal liability?

FDA Workshop

Panel 2
**AI in Medicine**
Michael Goldbaum
Shiley Eye Institute, University of California San Diego
Origins

• William Gray Water
  – Machina speculatrix
  – Connections between few brain cells yield complex behavior
• John McCarthy
  – Coined “artificial intelligence”
  – Science and engineering of making intelligent machines

AI themes

• Knowledge engineering/acquisition
• Ontogenies, terminologies
• Natural language
• Temporal information management
• Case-based reasoning
• Distributed, cooperative systems
• Management of uncertainty
• Machine-learning data mining
• Image processing
• Bioinformatics
Natural Language Processing

• Natural language sentences
  – Translation
• Extension to
  – Structure and patterns of concepts
  – Extract information of adverse drug events from narrative parts of EMRs
  – Epidemic surveillance from web news and social media

Management of Uncertainty

• Reasoning under uncertainty
• Expert systems
• Bayesian networks
• Inferencing algorithms
• Knowledge acquisition

Figure 5: Influence diagram, manifestations in vascular diseases
Machine learning & Data mining

- Computers that learn from data (vs being “taught”)
- Artificial neural networks
- Connection of nodes
  - Units and weighted connections
    - Feature set: Dendrites
    - Processor: Neuron body
    - Output: Axon
- Decision tree learning
  - CART
  - Random forest trees
- Back propagation
  - Learning adjusts connection weights
  - Multilayer perceptron
    - Deep learning neural networks

Image processing

- Image segmentation
- Object classification
- Grammar
  - Objects:images::words:sentences
- Context-based image retrieval
- Image interpretation
  - Segmentation → objects classification → image interpretation
  - Deep learning merges steps into a single classifier
Generational Perception of AI

“She thinks it’s a touchscreen.”

FDA Workshop

Panel 2

Cloud

Michael Goldbaum
Shiley Eye Institute, University of California San Diego
Cloud Computing

• Definition
  – Web-based technology where
  – Users share hardware and software in the cloud
• Service providers
  – Amazon Web Services
  – Google Compute Engine
  – Windows Azure
  – Aruba Cloud
• Can provide
  – Software and support platforms for software
  – Database for storage
    • Aggregating and harmonizing data
  – Analysis
    • Compute nodes for calculation
  – System infrastructure development

Software Tools for Cloud

• Web client
  – Application framework manages clinical use interaction through browser
• Web service
  – Services supporting data
    • Submission
    • Analysis
    • Retrieval of results
• Validation
  – User try common process on their data
  – Users apply their processes on common data
• User
  – User information
  – Authentication
Security

• EU General Data Protection Regulation
  – EUGDPR.org

• Access
  – Authorized users
  – 2 factors, e.g., DUO

• Transmission
  – HTTPS = hypertext transfer protocol
  – SPTP = secure transfer protocol
  – SCP = Secure copy protocol
  – VPN = Virtual private network

• Person going rogue

FDA Workshop

Panel 2
Who Does the Interpretation
Michael Goldbaum
Shiley Eye Institute, University of California San Diego
Three Types of Interpretation

• Machine does interpretation
  – Machine learning classifier
  – Deep learning
  – Physician assist
  – Available 24/7
  – Consistent
  – Black box

• Third party doctor reads results
  – No interface to patient
  – Domain expertise
  – Not 24/7
  – Inconsistent
    • Affected by mood, alertness, bias

• Patient’s regular doctor reads
  – Interface physician and patient
  – Not 24/7
  – Inconsistent
    • Affected by mood, alertness, bias

FDA Workshop

Panel 2
Interfacing between Eyecare and Non-Eyecare Professionals
Michael Goldbaum
Shiley Eye Institute, University of California San Diego
Perceptions of Communication

<table>
<thead>
<tr>
<th>Table 1</th>
<th>GPs’ and specialists’ perceptions on aspects of communication (17)</th>
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<tbody>
<tr>
<td></td>
<td>GPs agree</td>
</tr>
<tr>
<td>GPs telephone accessibility is good</td>
<td>85.3</td>
</tr>
<tr>
<td>Referral letter of GP is of good quality</td>
<td>—</td>
</tr>
<tr>
<td>Questions are addressed by the specialist</td>
<td>50.0</td>
</tr>
<tr>
<td>GPs follow the advice given by the specialist</td>
<td>92.2</td>
</tr>
<tr>
<td>Specialist letter is sent back in a timely manner</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Communication in healthcare: a narrative review of the literature and practical recommendations

P. Vermeire, D. Vandijk, S. Degroote, R. Delaney, R. Verheugen, E. Wouters, G. Hubert, S. Van Den Bergh, W. Buytaert, D. Vogels


Interface

• Goal: to overcome incommunicable silos in medical records
• Interface between eye care to non-eye care professionals
• Equivalence to professional-to-professional communication
• Different from concept of physician-to-patient
Methods of communication

• Hard copy
• Telephone/cell phone
• email
• Electronic medical records
• Multidiscipline team
• Social networks

Hard copy

• Letter
• Patient carries information
  – Paper
  – Thumb drive/DVD
• In-hospital consult
• Translation

• Disadvantages
  – Time consuming
  – No proof of receipt
Phone (Cell Phone)

• Voice
  – Recipient must be found and available
  – Interactive
  – Proof of receipt

• Message
  – Invariant to time, place, geography
  – Can be interactive
  – No proof or receipt

email

• Security

• Invariant to time, place, geography
Electronic Medical Records

- Professional-to-professional note
- Autopopulated report
  - Template
  - Letter
- Holistic view of patient
- DICOM-like interface for communication between different EMRs

- Disadvantages
  - Access to EMR is necessary
  - No proof of receipt

Professional Team

- Multidiscipline team
  - Time consuming
  - Location specific, or
  - Conference call or Skype
Social Networks
Professional Networks

• Good way to distribute knowledge