Review of Normative Database Construction in Available OCT Models

Robert Fechtner, MD
Disclosure

No financial interest in any of the content of this presentation.
What’s in a word?

- Normative database
- Reference database
What is the database for?

• Serves as a reference for new examinations
• Can determine a percentile rank for a calculated (measured) parameter (like a test score on a standardized test)
• It is a tool and results must be interpreted in a clinical context
What the database can answer

• In what percentile does the measurement fall compared with the reference population?
What the database cannot answer?

• Does one have disease or not?
• Normal, borderline, abnormal (in any other than a statistical sense)
• (But if designed correctly one is more likely to have disease at the tail end of the distribution.)
What is a reference database?

- Who is in the database?
- Who made the decision to include or exclude?
- Based on what criteria?
Resources Accessed
FDA Resources

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.92(a)(3)) that is not subject to premarket approval.

Learn more...

Search Database

510K Number: K
Model
Applicant Name
Device Name
Panel
Decision
Decision Date

Clear/Approved IVD Products
Expedited Review
Third Party Reviewed
Product Code

Other Databases
- 510(k)
- Registration & Listing
- Adverse Events (MAUDE)
- Recalls
- Premarket Approvals (PMAs)
- Inspections
- Device Classification
- Standards
- Total Product Life Cycle
- CFR Title 21
- Radiation-Emitting Products
- X-Ray Assembler
- Medsun Reports
- CLIA
<table>
<thead>
<tr>
<th>Device Name</th>
<th>Applicant</th>
<th>510(K) Number</th>
<th>Decision Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus Photo</td>
<td>Carl Zeiss Meditec Inc</td>
<td>K112184</td>
<td>06/18/2012</td>
</tr>
<tr>
<td>Envisu Spectral Domain Ophthalmic Imagin</td>
<td>Bioptigen, Inc.</td>
<td>K120057</td>
<td>05/11/2012</td>
</tr>
<tr>
<td>Cirrus Hd-Oct With Retinal Nerve Fiber L</td>
<td>Carl Zeiss Meditec Inc</td>
<td>K111157</td>
<td>01/19/2012</td>
</tr>
<tr>
<td>SpectraSIS Anterior Segment Module (Spec)</td>
<td>Heidelberg Engineering GmbH</td>
<td>K113129</td>
<td>11/08/2011</td>
</tr>
<tr>
<td>RyVue Cam With Corneal Power Upgrade</td>
<td>Optovue, Inc.</td>
<td>K111505</td>
<td>09/08/2011</td>
</tr>
<tr>
<td>SpectraSIS HRA+Oct, SpectraSIS Fa_oct. S</td>
<td>Heidelberg Engineering</td>
<td>K101223</td>
<td>10/01/2010</td>
</tr>
<tr>
<td>Ivue, Model 100</td>
<td>Optovue, Inc.</td>
<td>K091404</td>
<td>04/22/2010</td>
</tr>
<tr>
<td>Cirrus Hd-Oct With Retinal Nerve Fiber L</td>
<td>Carl Zeiss Meditec Inc</td>
<td>K083291</td>
<td>05/05/2009</td>
</tr>
<tr>
<td>3d Oct-1000 Mark II Optical Coherence To</td>
<td>Topcon Medical Systems, Inc.</td>
<td>K083316</td>
<td>03/13/2009</td>
</tr>
</tbody>
</table>
Optovue RTVue

- “The Normative Database for the RTVue” - Michael J. Sinai, PhD (K101505) (software version 6.0)
- FDA Website 510(K) Summary K101505
- Dr. Qienyuan Zhou – personal communication
CZM Cirrus HD OCT

- FDA Website 510(K) Summary K111157
- Dr. Vincent Michael Patella – personal communication
Heidelberg Spectralis

• Spectralis user guide section 11.8.5 “Normative Database” (page 250-251)
• FDA Website 510(K) Summary K101223
• Dr Gerhard Zinser – personal communication
## Database Subject Collection

<table>
<thead>
<tr>
<th>Study Sites</th>
<th>RTVue</th>
<th>Cirrus</th>
<th>Spectralis</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 worldwide contributed data (15 initially recruited):</td>
<td>6 USA</td>
<td>1 China</td>
<td>1 Germany</td>
</tr>
<tr>
<td>6 USA</td>
<td>1 China</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 India</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 England</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Subjects</td>
<td>480</td>
<td>284</td>
<td>201</td>
</tr>
<tr>
<td>Subject Ethnicity</td>
<td>Caucasian</td>
<td>African descent</td>
<td>Caucasian</td>
</tr>
<tr>
<td></td>
<td>African descent</td>
<td>Chinese</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>European descent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>Hispanic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>other</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Age</td>
<td>18-84</td>
<td>19-84</td>
<td>18-78</td>
</tr>
<tr>
<td>Significance limits include</td>
<td>RNFL thickness</td>
<td>peripapillary RNFL</td>
<td>RNFL thickness</td>
</tr>
<tr>
<td></td>
<td>Ganglion cell complex (GCC)</td>
<td>thickness for the optic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macular retinal thickness</td>
<td>nerve head scan cube</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>optic nerve parameters</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>macular ganglion cell +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPL thickness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>macular retinal thickness</td>
<td></td>
</tr>
</tbody>
</table>
## Exclusions

<table>
<thead>
<tr>
<th></th>
<th>RTVue</th>
<th>Cirrus</th>
<th>Spectralis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular History</strong></td>
<td>active ocular disease&lt;br&gt;congenital abnormalities&lt;br&gt;anatomic narrow angle&lt;br&gt;glaucoma or suspect&lt;br&gt;diabetic retinopathy&lt;br&gt;uncomplicated cataract surgery within 6 month other previous intraocular surgery</td>
<td>vitreo-retinal disease, uncomplicated cataract and/or refractive surgery eye within 12 months&lt;br&gt;any complicated eye surgery&lt;br&gt;amblyopia&lt;br&gt;glaucoma, ocular hypertension, glaucoma suspect&lt;br&gt;angle closure, disc hemorrhage infection or inflammation in the eye</td>
<td>Glaucoma&lt;br&gt;vitreal, retinal or choroidal diseases or disease of the optic nerve&lt;br&gt;any intraocular disease prior intraocular surgery (except cataract surgery)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td>leukemia&lt;br&gt;AIDS&lt;br&gt;dementia&lt;br&gt;multiple sclerosis&lt;br&gt;arteriosclerosis</td>
<td>leukemia&lt;br&gt;AIDS&lt;br&gt;dementia&lt;br&gt;multiple sclerosis&lt;br&gt;diabetes mellitus&lt;br&gt;uncontrolled systemic hypertension</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>glaucoma 1(^{st}) degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>hydroxychloroquine or chloroquine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Examination Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RTVue</th>
<th>Cirrus</th>
<th>Spectralis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refraction</strong></td>
<td>outside +/- 8 D sph, +/- 2 D cyl</td>
<td>outside -12 D to +8 D sph</td>
<td>outside -7 D to +5 D sph</td>
</tr>
<tr>
<td><strong>IOP</strong></td>
<td>&lt; 22 mmHg</td>
<td>&lt; 22 mmHg</td>
<td>≤ 21 mmHg</td>
</tr>
<tr>
<td><strong>Visual Acuity</strong></td>
<td>BCVA 20/30 or better in each eye</td>
<td>no less than 20/40 Snellen or Snellen equivalent either eye</td>
<td>0.7 or better (~20/30)</td>
</tr>
<tr>
<td><strong>Optic nerve and RNFL</strong></td>
<td>The appearance of the optic disc was not used as an exclusion criterion</td>
<td>no disc hemorrhage, RNFL defects</td>
<td>normal appearance of optic disc - 2 examiners</td>
</tr>
<tr>
<td><strong>Visual Field</strong></td>
<td>normal Humphrey 24-2 white on white test (&lt;25% FN, FP, FL) normal GHT (normal Octopus visual field also accepted)</td>
<td>normal Humphrey 24-2 Visual Field (15% or less FN, FP, FL) (normal program 30-2 also accepted)</td>
<td>Normal visual field based on FDT, Octopus or Goldman perimetry</td>
</tr>
</tbody>
</table>
Structure

- Normal
- Borderline
- Abnormal
Function

- :: < 5%
- ● < 2%
- ●● < 1%
- ●●● < 0.5%
- △ P < 5% DETERIORATION
- ▲ P < 5% (2 CONSECUTIVE)
- ▲▲ P < 5% (3+ CONSECUTIVE)
- X OUT OF RANGE
Structure?

- ≥5%
- <5%
- <1%
The Question of Generalizability

Example

The Cirrus HD-OCT normative database comprised 284 subjects of 527 subjects screened for inclusion.

240/527 (46%) were disqualified for the following reasons:

138/527 (26%) abnormal or unreliable visual field examination findings

40/527 (8%) posterior pole pathology

30/527 (6%) study-related medical issues
Have we sufficiently re-examined assumptions underlying current approach?
Who should be included?

Can/should optic nerve abnormality be an exclusion?
Who should be included?

Should medical conditions be an exclusion?
Who should be included?

Is visual field required? What is normal?
The more exclusions, the greater the chance of a “supernormal” reference population

Is this desirable?
Why not be inclusive?

Would predictably improve specificity.
What if all were included?

- Unbiased population-based cohort
- Some with disease would be included
- Reference database would still resemble general population if large enough and disease with low prevalence
- Remains a percentile measure
Reference Database

• Serves as a reference for new examinations
• Can determine a percentile rank for a calculated (measured) parameter (like a test score on a standardized test)
• It is a tool and results must be interpreted in a clinical context
The value of expert consensus

• Expertise resides in FDA and AGS
• Provide guidance for acceptable reference database construction
• Some basic questions must be addressed
• Model protocol for a basic reference database