68\textsuperscript{Gallium Information Session

Michael Graham, PhD, MD
Dominique Delbeke, MD, PhD
David Dick, PhD
John Sunderland, PhD
Welcome and Meeting Overview
Imaging with $^{68}$Ga-DOTA-XXX

Michael M. Graham, PhD, MD
University of Iowa

Dominique Delbeke, MD, PhD
Vanderbilt University

Images done at 90 min.

Germany
How to Choose which one

• Accuracy
• Simplicity of Synthesis
• Patent Status
• Precursor availability
Table 1  Affinity profiles of DOTA-octapeptides (IC$_{50}$) for hsst1–5 receptors. IC$_{50}$ values are in nmol/l (mean±SEM).

<table>
<thead>
<tr>
<th>Compound</th>
<th>hsst1</th>
<th>hsst2</th>
<th>hsst3</th>
<th>hsst4</th>
<th>hsst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-28</td>
<td>3.8±0.3 (10)</td>
<td>2.5±0.3 (11)</td>
<td>5.7±0.6 (10)</td>
<td>4.2±0.3 (11)</td>
<td>3.7±0.4 (11)</td>
</tr>
<tr>
<td>Ga-DOTA-NOC</td>
<td>&gt;10,000 (3)</td>
<td>1.9±0.4 (3)</td>
<td>40.0±5.8 (3)</td>
<td>260±74 (3)</td>
<td>7.2±1.6 (3)</td>
</tr>
<tr>
<td>In-DOTA-NOC</td>
<td>&gt;10,000 (3)</td>
<td>2.9±0.1 (3)$^b$</td>
<td>8.0±2.0 (3)$^b$</td>
<td>227±18 (3)</td>
<td>11.2±3.3 (3)</td>
</tr>
<tr>
<td>Lu-DOTA-NOC</td>
<td>&gt;10,000 (3)</td>
<td>3.4±0.4 (3)$^b$</td>
<td>12.0±3.3 (3)$^b$</td>
<td>747±47 (3)$^b$</td>
<td>14.0±3.5 (3)$^b$</td>
</tr>
<tr>
<td>In-DOTA-BOC</td>
<td>&gt;1,000 (2)</td>
<td>4.4±0.4 (3)$^b$</td>
<td>6.8±0.3 (3)$^b$</td>
<td>ND</td>
<td>10.5±1.5 (3)$^b$</td>
</tr>
<tr>
<td>Lu-DOTA-BOC</td>
<td>&gt;1,000 (2)</td>
<td>4.0±0.4 (3)$^b$</td>
<td>6.3±0.2 (3)$^b$</td>
<td>591±88 (2)</td>
<td>6.5±0.1 (3)$^b$</td>
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<tr>
<td>Ga-DOTA-BOC</td>
<td>700±300 (2)</td>
<td>1.7±0.2 (3)</td>
<td>10.5±0.5 (3)</td>
<td>ND</td>
<td>4.4±1.2 (3)</td>
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<tr>
<td>Y-DOTA-NOC-ATE</td>
<td>&gt;1,000 (2)</td>
<td>4.2±2.0 (3)</td>
<td>47±1 (3)</td>
<td>ND</td>
<td>12±1 (3)$^b$</td>
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<tr>
<td>Lu-DOTA-NOC-ATE</td>
<td>&gt;1,000 (2)</td>
<td>3.6±0.3 (3)$^b$</td>
<td>30±2 (3)</td>
<td>ND</td>
<td>15±1 (3)$^b$</td>
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<tr>
<td>Ga-DOTA-NOC-ATE</td>
<td>&gt;1,000 (2)</td>
<td>2.6±0.3 (3)</td>
<td>113±80 (2)</td>
<td>53±30 (2)</td>
<td>25±4 (3)</td>
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<tr>
<td>Y-DOTA-BOC-ATE</td>
<td>&gt;1,000 (2)</td>
<td>2.9±0.3 (3)$^b$</td>
<td>23±1 (3)</td>
<td>ND</td>
<td>7.8±2.0 (3)</td>
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<td>Ga-DOTA-BOC-ATE</td>
<td>&gt;1,000 (2)</td>
<td>2.0±0.2 (3)</td>
<td>33±23 (2)</td>
<td>35±24 (2)</td>
<td>19.5±13.0 (2)</td>
</tr>
<tr>
<td>Somatostatin-28$^a$</td>
<td>5.2±0.3 (19)</td>
<td>2.7±0.3 (19)</td>
<td>7.7±0.9 (15)</td>
<td>5.6±0.4 (19)</td>
<td>4.0±0.3 (19)</td>
</tr>
<tr>
<td>Ga-DOTA-TOC$^a$</td>
<td>&gt;10,000 (3)</td>
<td>2.5±0.5  (3)</td>
<td>613±140</td>
<td>&gt;1,000 (3)</td>
<td>73±21 (3)</td>
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<tr>
<td>Y-DOTA-TOC$^a$</td>
<td>&gt;10,000 (3)</td>
<td>11.0±1.7  (3)</td>
<td>389±135</td>
<td>&gt;10,000 (3)</td>
<td>114±29 (3)</td>
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<tr>
<td>Ga-DOTA-OC$^a$</td>
<td>&gt;10,000 (3)</td>
<td>7.3±1.9  (3)</td>
<td>120±45</td>
<td>&gt;1,000 (3)</td>
<td>60±14 (3)</td>
</tr>
<tr>
<td>Y-DOTA-OC$^a$</td>
<td>&gt;10,000 (3)</td>
<td>20±2$^b$</td>
<td>27±8$^b$</td>
<td>&gt;10,000 (3)</td>
<td>57±22 (3)</td>
</tr>
<tr>
<td>Ga-DOTA-TATE$^a$</td>
<td>&gt;10,000 (3)</td>
<td>0.20±0.04 (3)</td>
<td>&gt;1,000 (3)</td>
<td>300±140</td>
<td>377±18 (3)</td>
</tr>
<tr>
<td>Y-DOTA-TATE$^a$</td>
<td>&gt;10,000 (3)</td>
<td>1.6±0.4$^b$ (3)</td>
<td>&gt;1,000 (3)</td>
<td>523±239</td>
<td>187±50$^b$ (3)</td>
</tr>
</tbody>
</table>

- 78 sites were found positive with $^{68}$Ga-DOTATATE versus 79 regions with $^{68}$Ga-DOTATOC
- Within the defined regions, 254 lesions were detected with $^{68}$Ga-DOTATATE versus 262 lesions with $^{68}$Ga-DOTATOC (P =0.012).
- On average, 8.2 lesions were found per patient with $^{68}$Ga- DOTATATE versus 8.5 lesions with $^{68}$Ga-DOTATOC.
Current North American Activity

• DOTA-TOC
  – Iowa (MGH)

• DOTA-TATE
  – Vanderbilt, UCLA, Excel Therapeutics (NIH, Stanford, MD Anderson)

• DOTA-NOC
  – Indiana, Edmonton
University of Iowa Experience

Ga-68 DOTA-TOC

RDRC: N=5
IND: N =120
Repeatability of Ga-68 DOTATOC PET Imaging in Neuroendocrine Tumors.
Pancreas (2013) in press
Unknown Primary with Metastatic NET to Liver and Bones, Negative Octreoscan and CT for Primary
Indications for Ga-68 DOTATOC (N=89) [Cost-recovery IND study at Iowa]
Scan Results (Needs to be updated)

Diagnosis of NET
• Ga-68 DOTATOC positive in only 1/22 patients presenting with symptoms/labs suggestive of elevated serotonin without diagnosis of NET (false positive)

Unknown Primary
• Ga-68 DOTATOC identified primary tumor in 14/20 pts with metastatic disease, 7 have gone to surgery to remove primary. 2 others confirmed by biopsy. Conventional imaging found 3.

Initial staging (13)
Restaging (34)

<table>
<thead>
<tr>
<th>First author</th>
<th>Number</th>
<th>Median OS (months)</th>
<th>5y survival</th>
<th>Number</th>
<th>Median OS (months)</th>
<th>5y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Givi</td>
<td>66</td>
<td>108</td>
<td>81%</td>
<td>18</td>
<td>50</td>
<td>21%</td>
</tr>
<tr>
<td>Strosberg</td>
<td>100</td>
<td>110</td>
<td>74%</td>
<td>35</td>
<td>88</td>
<td>46%</td>
</tr>
<tr>
<td>Ahmed</td>
<td>209</td>
<td>119</td>
<td>74%</td>
<td>76</td>
<td>57</td>
<td>46%</td>
</tr>
<tr>
<td>Søreide</td>
<td>53</td>
<td>139</td>
<td>75%</td>
<td>12</td>
<td>69</td>
<td>28%</td>
</tr>
<tr>
<td>Norlen</td>
<td>493</td>
<td>139</td>
<td>75%</td>
<td>86</td>
<td>69</td>
<td>28%</td>
</tr>
<tr>
<td>Van der Horst-Schriever</td>
<td>27</td>
<td>75</td>
<td>57%</td>
<td>49</td>
<td>52</td>
<td>44%</td>
</tr>
</tbody>
</table>

| Total                 | 948    | 110.2              | 72%         | 276    | 63.2               | 35%         |

Available data suggest a possible benefit of resection of the primary lesion in patients with un-resectable liver metastases, but the studies have several limitations and the results should therefore be considered with caution.
68Ga-DOTATATE: The Vanderbilt Experience

Dominique Delbeke, MD, PhD
Ron Walker, MD (Imaging)
Eric Liu, MD (surgery)
Jeff Clanton, RD (Radiopharmacy)

68Ga Consortium meeting, SNMMI Annual meeting
June 11, 2013, Vancouver, Canada
Clinical Trial at Vanderbilt/VAMC

$^{68}$Ga-DOTATATE Manufacturing

- Equipment needed: Radiochemistry laboratory
  - $^{68}$Ge/$^{68}$Ga generator:
    - Eckert & Ziegler (Berlin, Germany)
  - Precursor: DOTATATE from ABX (Advanced Biochemical Compounds, Radelberg, Germany)
  - Quality control equipment
Clinical Trial at Vanderbilt/VAMC

$^{68}$Ga-DOTATATE PET/CT Imaging Protocol

- **Administered activity:**
  - 50 microg or less of the peptide
  - Average activity: 196 MBq (5.3 mCi)
  - Range: 159-222 MBq (4.3-6.0 mCi)

- **PET/CT protocol for image acquisition: same as $^{18}$F-FDG**
  - Field of view: from vertex to mid-thighs
  - Uptake time: 60 +/- 10 min (dynamic for dosimetry)
  - CT: Low-mAs helical CT without contrast
  - PET: 3D 4 min/bed
Clinical Trial at the TN Valley VA Healthcare System:

$^{68}\text{Ga-DOTATATE}$ PET/CT Imaging in Lung Nodule
(Funded by a VA Merit Grant)

Human dosimetry analysis under RDRC approval for biodistribution investigation:

- Have been completed in 6 patients.
- No observed adverse events in the immediate or delayed time frames, with follow-up of one year.
- Critical organ: Spleen followed by the bladder, kidneys, liver.
- Whole body dosimetry:
  - Similar to the closely related $^{68}\text{Ga-DOTATOC}$ and NOC.
  - Less than $^{111}\text{In-DTPA-octreotide}$ or $^{18}\text{F-FDG}$

<table>
<thead>
<tr>
<th></th>
<th>$^{68}\text{Ga-DOTATATE}$</th>
<th>$^{68}\text{Ga-DOTATOC}$</th>
<th>$^{68}\text{Ga-DOTANOC}$</th>
<th>$^{111}\text{In-Octreotide}$</th>
<th>$^{18}\text{F-FDG}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Dose per scan</td>
<td>4.8 mSv</td>
<td>4.3 mSv</td>
<td>3.1 mSv</td>
<td>5.9 mSv</td>
<td>7 mSv</td>
</tr>
</tbody>
</table>

Clinical Trial at Vanderbilt: $^{68}$Ga-DOTATATE PET/CT Imaging in Neuroendocrine Cancer

- VUMC has an IND (Investigational New Drug application) from the US FDA (#111972) for the use of $^{68}$Ga-DOTATATE in evaluation patients with advanced NET
- The study is investigator-initiated
- Funding:
  - Investigational procedures are not reimbursed by Medicare
  - FDA grants permission to charge insurances and patients for the experimental drug ($^{68}$Ga-DOTATATE): Application to the US FDA for “cost-recovery”
  - Imaging procedure is also charged.
Clinical Trial at Vanderbilt: $^{68}$Ga-DOTATATE PET/CT Imaging in Neuroendocrine Cancer

- **Study purpose**: To determine the safety and efficacy of $^{68}$Ga-DOTATATE in patients with neuroendocrine cancer.
- **Patient Population**: From 5/2011 to 5/2013, 80 adult patients who had suspected or known NET
  - Need of diagnosis 11% (9/80)
  - Need of staging 1% (1/80)
  - Need of restaging 88% (70/80)
    - Small bowel 56% (45/80)
    - Pancreas 16% (13/80)
    - Bronchial 9% (7/80)
    - Rectum 3% (2/80)
    - UP 4% (3/80)

www.clinicaltrials.gov: NCT01396382
Clinical Trial at Vanderbilt: $^{68}$Ga-DOTATATE PET/CT Imaging in Neuroendocrine Cancer

**Safety evaluation (NCI criteria):**

- **Patient observation and vital signs:** before $^{68}$Ga-DOTATATE administration and 3 hours after administration
  - blood pressure and heart rate
  - body temperature
  - pulse oximetry on room air
- **12 leads EKG:** pre-injection and 3 hours post administration
- **Laboratory tests:** pre-injection and 1 week post administration:
  - Tumor markers
  - Complete blood counts with differential
  - Electrolytes
  - Comprehensive metabolic panel: renal and liver function
Clinical Trial at Vanderbilt: $^{68}$Ga-DOTATATE PET/CT Imaging in Neuroendocrine Cancer

- **Summary of adverse experiences:** None
- **Interpretation of the $^{68}$Ga-DOTATATE images:**
  - High degree of inter-observer (n=3) agreement
    - Discordant findings between observers would have lead to a change in management in 1 of 80 patients
Clinical Trial at Vanderbilt: $^{68}$Ga-DOTATATE PET/CT Imaging in Neuroendocrine Cancer

- **Clinical efficacy analysis:** Change of patient’s management
  - No impact: 48% of patients
  - Inter-modality change: 42% (33/80)
    - Candidates for surgery: 15% (12/80), 2/3 UP
    - Not candidates for surgery: 4% (3/80), 1/9 diagnosis
    - Candidates for PRRT: 20% (16/80)
    - Not candidates for PRRT: 3% (2/80)
  - Intra-modality change: 10% (8/80)
    - Change in surgical plans: 3.5% (3/80)
    - Additional PRRT: 3.5% (3/80)
    - Refer to endoscopic ultrasound: 3% (2/80)

- **Conclusions:** change in patient’s management
  - Restaging NET: 57% (40/70)
  - Diagnosis: 11% (1/9)
The pathway towards approval
Ga-68 DOTA-TOC and DOTA-TATE

The Plan

• 1st step: Orphan drug designation
• CTN template documents
  • IND template for DOTA-XXX
  • Basic clinical and imaging protocol
  • Data collections forms
• FDA meeting for Confirmatory trial
  • Population: pts with known disease
  • Change in management, biopsy results
  • Support w expanded access, cost-recovery IND
Important FDA Concepts

• Cost Recovery
• Expanded Access
• Orphan drug status
Cost Recovery

- FDA believes that in most cases the cost of an investigational drug in a clinical trial intended to support a marketing application is an ordinary cost of doing business.

- The purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of making certain drugs when clinical trials could not be conducted without charging because the cost of the drug.

- A sponsor authorized to charge for its drug in a clinical trial can only recover its direct costs.
Expanded Access IND

- The primary purpose is to diagnose, monitor, or treat a patient’s disease or condition, rather than characterize the safety and/or effectiveness of the investigational drug.

- The aim of expanded access is to facilitate the availability of the investigational new drug to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the patient’s disease or condition.
General Criteria for Expanded Access

• The patient has a serious or immediately life threatening disease or condition.

• There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.

• The potential patient benefit justifies the potential risks

• Providing the investigational drug for the requested use will not interfere with the clinical investigations that could support marketing approval
For expanded access, all of the following conditions exist:

- Use of the PET drug by the institution producing the PET drug is limited to use within that institution.

- The isotope properties (e.g., very short half-life) and nature of use (e.g., use is limited to a small niche population) of the PET drug preclude commercialization.

- There is no commercially available formulation of the PET drug.
Orphan Drugs

The FDA Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in USA (not more than 5 in 10,000 in EU)

• Fewer subjects needed in pivotal trial
• Application fees are waived
• Eligible for FDA grant funding
Summary

- Ga-68 DOTA-XXX provides an accurate way to image neuroendocrine tumors
- Used clinically in Europe for > 10 years
- Requires:
  - Ge-68 / Ga-68 generator, Precursor supply
  - Synthesis unit, Cost recovery IND
  - Radiochemist (or equivalent)
  - Referral source of neuroendocrine tumor patients
- NDA approval is likely with 5 years
$^{68}$Ga Generator Issues and Update Precursor Availability Status

David Dick, PhD
University of Iowa
Ga-68 Generators

- Cyclotron Company Ltd
  - Obninsk, Russia

- Eckert & Ziegler
  - Berlin, Germany

- iThemba Labs
  - Cape Town, South Africa

- ITG GmbH
  - Munich, Germany
Patent Expiration

• DOTATATE
  – US/Canada: Expires in 2015
  – Europe: Expires in 2014

• DOTATOC
  – US/Canada: Expires in 2014
  – Europe: Expires in 2015

• DOTANOC
  – US: Expires in 2022 (BioSynthema)
  – Everywhere else: expired
Precursor suppliers

• DOTATATE
  – ABX, Bachem

• DOTATOC
  – Bachem, IBD

• DOTANOC
  – ABX, piCHEM
Major QC Equipment for Ga-68 DOTATATE/TOC/NOC

- Gas Chromatograph
- HPLC with radiation detector
- radioTLC reader
- NaI Well Counter with MultiChannel Analyzer (MCA)
Cost Recovery IND Procedures

John Sunderland, PhD
University of Iowa
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Sec. 312.8 Charging for investigational drugs under an IND.

This is only about 2 pages of text, and relative to other CFR documents, this is quite understandable.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.8
Or do Google search of “IND Cost Recovery”
Cost Recovery for a Standard IND

APPLIES ONLY TO COST RECOVERY OF MANUFACTURE OF DRUG – NOT IMAGING

a) General criteria for charging.
   1) You have to follow the rules in b-d, and get written permission from FDA. Applies to IND and Expanded Access IND.

b) Charging in a clinical trial
   1) Clinical benefit over and above available drugs.
   2) Data will be useful in obtaining FDA approval.
   3) Demonstrate that you NEED to charge because of extraordinary costs.

d) Costs recoverable when charging for an investigational drug
   1) ONLY Direct Costs (labor, supplies equipment)
   2) NOT Indirect Costs
   3) must provide supporting documentation of expenses (Receipts, quotes…). The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.
Cost Recovery for an Expanded Access IND

APPLIES ONLY TO COST RECOVERY OF MANUFACTURE OF DRUG AND CERTAIN IND ADMINISTRATIVE COSTS—NOT IMAGING

(c) Charging for expanded access to investigational drug for treatment use

(i) Evidence of sufficient enrollment to complete trial
(ii) Evidence of adequate progress in the development of the drug for marketing approval; and
(iii) Information submitted under the general investigational plan (312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.
E-Mail from Lucie Yang, M.D., Ph.D.
CDER, FDA 2/14/12

Your question:
Can the sponsor of a traditional (clinical trial) IND or expanded access IND for a PET drug recover the costs not only of the drug (direct costs) but also the costs of image acquisition and image interpretation?

Our answer:
FDA authorizes cost recovery only for the drug. Seeking cost recovery for monitoring or supportive aspects (e.g. radiographic procedures) is beyond the FDA purview. Conceivably, these investigational costs may be charged to the patient, contingent upon the local IRB expectations.

Let me know if you need further clarification.

Thank you,
-lucie
Allowed Direct Costs

• Capital Expenses Depreciated:
  – Hot Cell, Synthesis Module (5 year depreciation or whatever you want. Break this cost down to $/patient based upon projected volume)

• Ge-68/Ga-68 Generator ($40K/6 months – Break this cost down to $/patient based upon projected volume)

• Synthesis Costs
  – Cassettes, Reagents, GMP Peptide, Vials… ($350)

• Personnel Costs
  – Radiochemists time (about 5 man hours/synthesis) ($300)

• QC Costs ($50)
Conclusion

Based upon the results of our testing and conversations with management, we can conclude that all costs included in the client calculation tie to invoices supplied without deviation. Furthermore, all formulae prepared by client have been recalculated and are correctly applied to the cost calculation.

With regard to the application of costs associated with this IND we can conclude that the calculation is consistent with the requirements of paragraphs (d)(1) of Code of Federal Regulations, Title 21, Volume 5, Part 312, Section 312.8.

Sincerely,

DRAFT
# Financial Modeling

## ACCOUNTING NET INCOME DOTATOC MODEL n page

### Regular Lab Depreciation Schedule:

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cost Scan</th>
<th>Linear</th>
<th>$1,300</th>
<th>$85,906</th>
<th>$200</th>
<th>$400</th>
<th>$600</th>
<th>$800</th>
<th>$1,000</th>
<th>$1,200</th>
<th>$1,400</th>
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<tbody>
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<td>50</td>
<td>1</td>
<td>$144,206</td>
<td>($191,206)</td>
<td>($173,206)</td>
<td>($155,206)</td>
<td>($137,206)</td>
<td>($119,206)</td>
<td>($101,206)</td>
<td>($83,206)</td>
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<td></td>
</tr>
<tr>
<td>60</td>
<td>1</td>
<td>$151,148</td>
<td>($207,548)</td>
<td>($185,948)</td>
<td>($164,348)</td>
<td>($142,748)</td>
<td>($121,148)</td>
<td>($99,548)</td>
<td>($77,948)</td>
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<tr>
<td>70</td>
<td>1</td>
<td>$17,181</td>
<td>($223,891)</td>
<td>($198,691)</td>
<td>($173,491)</td>
<td>($148,291)</td>
<td>($123,091)</td>
<td>($97,891)</td>
<td>($72,691)</td>
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### Hot Cell Depreciation

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<thead>
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<th>$40,000</th>
<th>$200</th>
<th>$400</th>
<th>$600</th>
<th>$800</th>
<th>$1,000</th>
<th>$1,200</th>
<th>$1,400</th>
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<tbody>
<tr>
<td>Net revenue</td>
<td>Net revenue</td>
<td>Year Net revenue</td>
<td>Net revenue</td>
<td>Net revenue</td>
<td>Net revenue</td>
<td>Net revenue</td>
<td>Net revenue</td>
<td>Net revenue</td>
</tr>
<tr>
<td>$165,034</td>
<td>$17,577</td>
<td>$25,181</td>
<td>$178,920</td>
<td>$185,863</td>
<td>$192,805</td>
<td>$199,748</td>
<td>$206,690</td>
<td>$213,636</td>
</tr>
</tbody>
</table>

### Depreciation Costs per Patient


### GA GENERATOR

| Generator Replacement | $403,662 | $338,862 | $274,062 | $209,262 | $144,462 | $79,662 | $14,862 | $9,605 | $4,348 |

### Generator Cost/Subject

| Cost/Subject | $1,204 |
Questions and Answers