

Appendix A Market Diffusion Interview Materials, Summaries, and Results

This appendix contains materials used to complete the forecasts of technology penetration for each of the seven tissue engineering projects we analyzed in this study. For the four in-depth case studies listed in Table 1-1, we conducted more in-depth case studies than for the remainder of the projects. For the in-depth case studies, we interviewed physicians to obtain data for the Bass diffusion model, as explained in Section 2. For the remainder of the companies, we collected diffusion estimates for the Bass model from the companies' representatives.

A.1 INTERVIEW MATERIALS

Figures A-1 through A-4 contain the clinical profiles we developed and provided to physicians prior to the interviews. We did not identify the company, either on the profile or during the interview.

Figure A-5 is a sheet of questions that we sent to the physicians along with the clinical profile. It was designed to prepare the physicians to answer our questions. Figure A-6 contains the informal interview guide that we used while interviewing the physicians over the telephone.

Table A-1 provides information about the physicians we interviewed. These physicians were recommended to us as experts in the treatment of the relevant diseases by ATP-sponsored companies, by associations such as the American Diabetes Association, or by other physicians.

A.2 DATA COLLECTED

Table A-2 contains the data that we collected from the physicians and company representatives for input to the model. For some of the projects, the physicians identified and provided market penetration estimates for a number of different populations. In these cases, we divided the eligible population into these segments and developed weighted averages for input to the Bass diffusion model. For example, for the project "Biopolymers for Tissue Repair," the total eligible population was 73,875; 33,825 adults and 40,050 children. Expert 1 forecasted a market cap of 25 percent for adults and 75 percent for children as his estimate for the market cap. Therefore, we used 38,494 as his forecast of the market cap for this technology.

Figure A-1. Clinical Profile for “Human Stem Cell and Hematopoietic Expansion Systems”

Many patients with dose-sensitive cancers are treated with high-dose chemotherapy and/or radiation. To enable the patient to survive this treatment, patients are treated with stem cell therapy to repair the damage to their hematopoietic system. In many cases, the stem cells are harvested from the patient prior to the myelotoxic treatment or from a donor via peripheral blood progenitor cell (PBPC) collection. PBPC requires the use of mobilization drugs that may have side effects for the patient or donor.

Assume that a new method for stem cell harvest is now available. This new method involves extracting a small quantity of bone marrow (a single aspirate) in a doctor’s office under local anesthesia. The aspirate is placed in a Cell Production System (CPS) which is fully automated for growing stem cells outside the human body. This method may reduce the probability that certain tumor cells will be reintroduced via the graft.

Please examine the clinical profile below and think about the current stem cell harvest techniques versus the new treatment we described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient, including all resources required for stem cell harvest:	No more than \$12,000.												
Likely alternative treatment and treatment cost:	Peripheral blood progenitor cell (PBPC) mobilization. \$12,000-\$20,000												
Risks/side-effects:	No drugs or procedures required to prepare the patient for the procedure prior to the time of the aspirate.												
Ease of use:	It is very easy to use and requires limited training.												
Expected outcomes of new treatment compared to likely alternative treatment:	<p>May reduce tumor cells in a graft by 10- to 70-fold versus the conventional methods.</p> <p>Other differences noted below.</p> <table border="1"> <thead> <tr> <th>Cell Source</th> <th>Care Episodes^a</th> <th>Procedure Time (Hours)</th> <th>Needle Sticks^b</th> </tr> </thead> <tbody> <tr> <td>PBPC mobilization and collection^c</td> <td>21</td> <td>39</td> <td>22</td> </tr> <tr> <td>CPS^d</td> <td>2</td> <td>1-3</td> <td>4-10</td> </tr> </tbody> </table> <p>Note: The numbers in the table include all procedures associated with stem cell procurement and administration.</p> <p>^aIncludes all outpatient, inpatient, and home care episodes.</p> <p>^bIncludes bone marrow aspirates, blood samples, catheter placements, and subcutaneous injections.</p> <p>^cBased on an average of three rounds of apheresis following cell mobilization injections.</p> <p>^dBased on data accumulated during confidential company’s pre-clinical research and trials.</p>	Cell Source	Care Episodes ^a	Procedure Time (Hours)	Needle Sticks ^b	PBPC mobilization and collection ^c	21	39	22	CPS ^d	2	1-3	4-10
Cell Source	Care Episodes ^a	Procedure Time (Hours)	Needle Sticks ^b										
PBPC mobilization and collection ^c	21	39	22										
CPS ^d	2	1-3	4-10										

Figure A-2. Clinical Profile for “Structurally New Biopolymers Derived from Alpha-L Amino Acids”

Currently, fractures of the shoulder, elbow, wrist and hand, knee, and ankle are fixed with metallic devices. Some fractures are also fixed with bioabsorbable materials. Assume that new devices—pins and screws made from a newly developed bioabsorbable material—have just become available. The new bioabsorbable material is made from a novel synthesis of tyrosine that avoids the problems associated with acids produced by the breakdown of existing bioabsorbable polymers. Also, the new pins and screw are stiffer than the current bioabsorbable alternative. The primary application for the pins and screws is orthopedic repair (fracture fixation).

The new bioabsorbable pins and screws are intended for use in the following types of fractures:

- shoulder (distal clavicle, acromion, glenoid rim, proximal humerus)
- elbow (humeral condyles or capitellum, olecranon, radial head or neck)
- wrist and hand (distal radius, carpal and metacarpal bones)
- knee (femoral and tibial condyles, patella)
- ankle (uni or bimalleolar, and severe with syndesmotic disruption)

Source: Böstman, O., E. Hirvensalo, E. Partio, P. Törmälä, and P. Rokkanen. 1991. “Impact of the Use of Absorbable Fracture Fixation Impacts on Consumption of Hospital Resources and Economic Costs.” *The Journal of Trauma* 31(10):1400-1403.

Please examine the clinical profile below and think about the current treatment for fracture fixation versus the new bioabsorbable treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	Surgery cost identical to defending treatment. Material cost expected to be \$50-\$150 per pin or screw.
Likely alternative treatment and treatment cost:	Surgery with metallic fixation devices (pins and screws): \$8-\$20 per device.
Expected outcomes of new treatment compared to likely alternative treatment:	<ul style="list-style-type: none"> ➤ Reduction in stress shielding and secondary fractures due to screw holes ➤ Elimination of removal surgery ➤ Reduced potential for tissue abrasion or device loosening and migration

Figure A-3. Clinical Profile for “Disease Treatment Using Living Implantable Microreactors”

Currently, most insulin-dependent diabetics are treated with daily insulin injections. Assume that a new treatment has just become available that uses porcine pancreatic transplant cells encased in microspheres to achieve tight glycemic control in insulin-dependent diabetics. The cells permit glucose, nutrients, electrolytes, oxygen, and bioactive products to pass but block immunocytes involved in transplant rejection. As the cells cease to function, the patient will require a booster injection of new cells. The cells are intended for treatment of all Type I diabetics and Type II diabetics who require daily insulin injections.

Please examine the clinical profile below and think about the current treatment for insulin-dependent diabetics versus the new treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	\$12,000 for initial implant and \$6,000/year for booster implants, which are required once or twice a year.
Likely alternative treatment and treatment cost:	Daily insulin injections: \$1,666/year
Expected outcomes of new treatment:	<p>The new treatment will achieve equal or superior outcomes as realized in the Diabetes Control and Complications Trial (DCCT). The DCCT demonstrated the benefits of tight glycemic control for insulin-dependent diabetics. Results of the trial showed:</p> <ul style="list-style-type: none"> ➤ 76% reduced risk of eye disease ➤ 50% reduced risk of kidney disease ➤ 60% reduced risk of nerve disease ➤ 35% reduced risk of cardiovascular disease
Other benefits:	<ul style="list-style-type: none"> ➤ Improved quality of life ➤ Reduces glucose monitoring to once a week ➤ Eliminates daily insulin injections ➤ Automatic insulin response to glucose ➤ No immunosuppression required ➤ Simple to administer
Ease of use:	Procedure will be an injection under ultrasound control, similar to amniocentesis; done on an outpatient basis. Requires a simple syringe.

Figure A-4. Clinical Profile for “Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules”

Currently, most insulin-dependent diabetics are treated with daily insulin injections. Assume that a new treatment has just become available that uses proliferated insulin-secreting human islet cells combined with a unique encapsulation technology to help patients achieve tight glycemic control. The encapsulation technology ensures adequate immunoprotection and biocompatibility with the human body. The cells are intended for treatment of Type I diabetics and Type II diabetics who require daily insulin injections. This new treatment eliminates the need for daily insulin injections.

Please examine the clinical profile below and think about the current treatment for insulin-dependent diabetics versus the new treatment described above. Then, answer the questions on the following page.

Expected cost of new treatment per patient:	\$10,000-\$15,000 per year
Likely alternative treatment and treatment cost:	Daily insulin injections: \$1,666/year
Expected outcomes of new treatment:	<p>The new treatment will achieve similar outcomes as realized in the Diabetes Control and Complications Trial (DCCT). The DCCT demonstrated the benefits of tight glycemic control for insulin—dependent diabetics. Results of the trial showed:</p> <ul style="list-style-type: none"> ➤ 76% reduced risk of eye disease ➤ 50% reduced risk of kidney disease ➤ 60% reduced risk of nerve disease ➤ 35% reduced risk of cardiovascular disease
Other benefits:	<ul style="list-style-type: none"> ➤ Improved quality of life ➤ Reduces glucose monitoring to once a week ➤ Eliminates daily insulin injections ➤ Automatic insulin response to glucose ➤ No immunosuppression required ➤ Simple to administer

Ease of use:	Product is injectable, an in-office treatment. Patient is placed under local anesthesia, sits for 3 hours, and then goes home. Patient makes a monthly visit to the doctor for monitoring. Treatment is once a year or once every two years.
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Figure A-5. Questions about the Clinical Profile

1. In thinking about the application that this therapy is intended for according to the profile you just read, what group of patients do you believe will be eligible to receive the treatment?

Please list by group, defining each group. For example, one group might consist of "Type II diabetic patients currently requiring daily insulin injections." Use as many groups as necessary.

Group A:

Group B:

Group C:

2. Given that Group A is eligible for this treatment, what percentage of patients in this group do you think will actually receive the treatment?

Please provide this percentage for each of the first 5 years that the treatment is available.

Group A:

_____ % _____ % _____ % _____ % _____ %
 (year 1) (year 2) (year 3) (year 4) (year 5)

Group B:

_____ % _____ % _____ % _____ % _____ %
 (year 1) (year 2) (year 3) (year 4) (year 5)

Group C:

_____ % _____ % _____ % _____ % _____ %
 (year 1) (year 2) (year 3) (year 4) (year 5)

Figure A-6. Physician Interview Guide

This interview is part of a study that RTI is doing for the National Institute of Standards and Technology (NIST). NIST has asked us to talk with clinical experts about the expected market acceptance of a number of new biotechnologies.

Introduction

1. First, can you please tell me about your particular affiliation?
 - a. research organization, hospital or clinic, private or group practice, government, etc.
 - b. type of patient base you see (if appropriate)
 - c. number of years you have been in your present position, current title
 - d. your affiliation with the biotechnology company

Estimating the Eligible Population

Please examine the clinical profile of the treatment, including the target patient profile and the expected costs and outcomes of the treatment.

1. In thinking about the application that this therapy is intended for according to the profile we sent you, what group or groups of patients do you believe are eligible to receive the treatment?
 - ✓ describe patient cohorts (e.g., by age, severity of disease, type of disease, receiving a certain treatment, etc.)
 - ✓ Would these patients all be eligible for the defending treatment as we have defined it on the profile?
2. Do you think the population of eligible patients will change over time, or will the number of eligible patients remain constant over the next 10 years? How will it change?

(continued)

Figure A-6. Physician Interview Guide (continued)

Potential Barriers to Market Penetration and Market Penetration

1. What do you view as some of the barriers to this treatment’s widespread use? For example,

- ✓ physicians
- ✓ insurance companies
- ✓ patients
- ✓ hospitals
- ✓ costs

2. Who do you think will be most influential in determining whether this treatment becomes widely used or not (e.g., physicians, hospitals and managed care formularies, insurance companies, patients)?

3. Given that patients in group A (as you have defined it) are eligible for this treatment, and taking into account the barriers we just discussed, what percentage of the patients in group A do you think will actually *receive* the treatment?

Please provide this percentage for each of the first 5 years that the treatment is available.

_____ % _____ % _____ % _____ % _____ %
 (year 1) (year 2) (year 3) (year 4) (year 5)

4. Given that patients in group B (as you have defined it) are eligible for this treatment, and taking into account the barriers we just discussed, what percentage of the patients in group B do you think will actually *receive* the treatment?

Please provide this percentage for each of the first 5 years that the treatment is available.

_____ % _____ % _____ % _____ % _____ %
 (year 1) (year 2) (year 3) (year 4) (year 5)

Table A-2. Data Collected from Physician and Company Interviews

Eligible Population	Percentage of Population Receiving Treatment					Market Cap
	Year 1	Year 2	Year 3	Year 4	Year 5	
<i>Stem Cell Expansion</i>						
Autologous BMTs	4%	10%	15%	25%	—	—
Multicyclic chemotherapy	10%	20%	25%	30%	40%	—
Autologous BMTs	1%	5%	10%	10%	10%	100%
Multiple-course cancer therapy	1%	5%	10%	20%	20%	20%
Cord blood transplants	1%	10%	20%	50%	50%	100%
Chemotherapy + autologous stem cell support	3%	8%	15%	25%	35%	—
Chemotherapy + cord blood support	3%	8%	15%	20%	20%	100%
Dose intensive therapy	3%	8%	15%	25%	40%	100%
Chemotherapy and allogeneic stem cell support	3%	8%	15%	20%	20%	100%
<i>Biopolymers for Tissue Repair</i>						
Adults (five fracture sites)	1%	3%	5%	10%	15%	25%
Pediatric (all fractures)	2%	6%	10%	20%	30%	75%
Adults (five fracture sites)	25%	40%	55%	70%	75%	75%
Adults	10%	10%	10%	20%	20%	20%
Pediatric	10%	10%	10%	10%	10%	10%
<i>Living Implantable Microreactors</i>						
Type I diabetics	1%	5%	10%	10%	10%	10%
10% Type II diabetics	1%	10%	15%	15%	15%	15%
Type I children under 10 years of age	2%	2%	2%	5%	10%	100%
Type I over puberty and with complications	20%	25%	30%	40%	50%	100%
Type I over puberty with no complications	10%	10%	10%	20%	30%	100%
Type II insulin-dependent with disease for ≥10 years	2%	2%	2%	5%	10%	100%
Type I diabetics	3%	7%	15%	30%	50%	95%
Type II diabetics (ins-dep.) < age 50	1%	2%	4%	20%	25%	25%

(—) denotes missing value.

(continued)

Table A-2. Data Collected from Physician and Company Interviews (continued)

Eligible Population	Percentage of Population Receiving Treatment					Market Cap
	Year 1	Year 2	Year 3	Year 4	Year 5	
<i>Proliferated Human Islets</i>						
Type I diabetics	1%	5%	10%	10%	10%	10%
10% Type II diabetics	2%	10%	15%	20%	20%	20%
Type I children under 10 years of age	2%	2%	2%	5%	10%	100%
Type I over puberty and with complications	20%	25%	30%	40%	50%	100%
Type I over puberty with no complications	10%	10%	10%	20%	30%	100%
Type II insulin-dependent with disease for ≥10 years	2%	2%	2%	5%	10%	100%
Type I diabetics	3%	7%	15%	30%	50%	95%
Type II diabetics (ins-dep.) < age 50	1%	2%	4%	20%	25%	25%
<i>Biomaterials for Clinical Prostheses</i>	9%	20%	30%	40%	50%	75%
<i>Gene Therapy Applications</i>	10%	25%	40%	50%	55%	55%
<i>Universal Donor Organs</i>	10%	20%	30%	40%	50%	75%

(—) denotes missing value.

A.3 KEY FINDINGS FROM INTERVIEWS

We highlight key findings from the physician interviews by project.

Stem Cell Expansion

- ▶ In addition to autologous bone marrow transplants (BMTs), physicians believed this procedure would be useful for patients receiving multicyclic subablative chemotherapy and umbilical cord stem cell transplants.
- ▶ Two physicians stated that there are technical barriers to using this treatment for allogeneic transplants due to graft rejection, graft versus host disease, and the inability to restore blood cells to the level they need to be.
- ▶ Barriers to this treatment's market success cited by physicians interviewed include the cost of capital equipment for health maintenance organizations (HMOs), hospitals, and BMT centers; the ease of training; and physicians' belief in the procedure's reliability to grow stem cells. One physician said that a disadvantage of the

treatment is that once the cell expansion has started, the cells will have to be used on a given date and cannot be “saved” until a later date, in the event that a patient is unable to undergo the transplant.

- Physicians and CEOs of hospitals and managed care organizations were cited as being most influential in determining whether the treatment will become widely used.
- Physicians stated that the possibility of reducing tumor cells in a graft will be extremely important in determining the treatment’s market acceptance; however, this factor will not be important in terms of modeling health outcomes.

Biopolymers for Tissue Repair

- Physicians noted the differences between the pediatric orthopedic market and the adult orthopedic market. The pediatric market has a high removal rate for pins (95 percent) because physicians are reluctant to leave pins in growing bone. However, the removal rate for adults is closer to 10 to 15 percent.
- One physician said that the only adult population this would be applicable for is healthy adult patients with low-load nondiaphyseal fractures.
- Barriers to this treatment that were cited included physicians’ concern, even if it is misinformation, about possible reactions to bioabsorbable materials versus inert metals; the ability to use bioabsorbables mechanically as easily as metals are used; the fact that biodegradable devices may not have the same degree of interfragmental compression; and the higher cost of bioabsorbable materials.
- One surgeon said that surgeons will be most influential in determining whether these devices become widely used *if* they find the devices comparable to the metal devices.

Living Implantable Microreactors

- Physicians believed that the eligible population is identical to that for VivoRx’s technology.
- The biggest barriers cited to this treatment’s widespread use are the fact that human and porcine islets are good reservoirs for retroviruses, and the long-term effects of porcine retroviruses are not known. Cost was also cited as a barrier.

Proliferated Human Islets

- Physicians confirmed that the eligible populations for this treatment are Type I diabetics and 10 percent of Type II diabetics (those who are insulin-dependent). The only group not eligible for this treatment is women who are pregnant or considering getting pregnant.

- One physician believes that children and young adults who are beyond puberty *and* have already shown some complications related to diabetes will be the ideal group for both VivoRx's and BioHybrid's treatments, since the medical community will do anything to prevent further complications in such young patients.
- One physician stated that if we can clone human cells, these should be better than porcine cells; however, there is a big reservoir of porcine cells, so availability should not be an issue.
- The biggest barriers cited to this treatment's widespread use include
 - ✓ cost, which far exceeds current diabetes therapy, especially for young parents with young (less than 10 years of age) diabetic children;
 - ✓ availability of tissue for transplantation;
 - ✓ the government, which may be overly restrictive in regulating the number of patients able to receive either therapy (VivoRx or BioHybrid);
 - ✓ pharmaceutical companies that are large producers of insulin and insulin-related products;
 - ✓ concerns about unrecognized malignant cell transmission; and
 - ✓ long-term immunological effects of this type of transplantation.
- Physicians predicted that the American Diabetes Association and professional endocrine societies will be influential in determining how widespread this treatment becomes. One physician believed it will be primarily patient-driven, because many patients will be willing to pay more for improving lifestyles (i.e., reduction in glucose monitoring).

A.4 RESULTS OF MODEL ESTIMATES

Table A-3 summarizes the results of our diffusion modeling. The forecasted estimate is the quantity of patients used in the model for estimating returns. The "high" and "low" columns are the end points of the 95 percent confidence intervals for the forecasts.

Table A-3. Summary Results

ATP Project	Year	Number of Patients		
		Forecast Estimate	95% Confidence Interval	
			High	Low
Human Stem Cell and Hematopoietic Expansion Systems in Tissue Engineering	1	665	665	665
	2	1,060	1,162	958
	3	1,674	2,002	1,373
	4	2,606	3,371	1,953
	5	3,976	5,477	2,750
	6	5,890	8,424	3,823
	7	8,384	11,996	5,224
	8	11,334	15,537	6,986
	9	14,424	18,318	9,098
	10	17,251	20,172	11,489
Structurally New Biopolymers Derived from Alpha-L-Amino Acids	1	8,173	8,173	8,173
	2	13,286	13,889	12,683
	3	20,007	21,525	18,500
	4	26,980	29,056	24,763
	5	31,977	33,494	29,942
	6	34,158	34,718	33,002
	7	34,744	34,874	34,289
	8	34,863	34,889	34,715
	9	34,885	34,890	34,840
	10	34,889	34,890	34,876
Disease Treatment Using Living Implantable Microreactors	1	65,498	65,498	65,498
	2	110,468	130,376	90,560
	3	183,271	252,047	124,436
	4	295,888	460,182	169,546
	5	457,310	755,608	228,401
	6	661,608	1,043,557	303,100
	7	874,437	1,175,873	394,507
	8	1,041,811	1,187,567	501,178
	9	1,134,485	1,187,113	618,454
	10	1,171,047	1,187,135	738,431

(continued)

Table A-3. Summary Results (continued)

ATP Project	Year	Number of Patients		
		Forecast Estimate	95% Confidence Interval	
			High	Low
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	1	63,711	63,711	63,711
	2	122,647	175,059	70,234
	3	202,286	339,115	78,109
	4	305,295	552,472	87,592
	5	430,677	779,403	98,978
	6	571,339	958,064	112,598
	7	713,520	1,053,241	128,820
	8	840,452	1,087,586	148,042
	9	939,509	1,097,188	170,678
	10	1,007,470	1,099,607	197,136
Fabrication of Clinical Prosthesis from Biomaterials	1	9,000	9,000	9,000
	2	19,493	22,777	16,209
	3	30,293	37,258	23,397
	4	40,629	50,442	30,376
	5	49,780	60,631	36,974
	6	57,277	67,321	43,050
	7	62,996	71,152	48,506
	8	67,102	73,145	53,292
	9	69,914	74,124	57,400
	10	71,773	74,591	60,862
Application of Gene Therapy to Treatment of Cardiovascular Diseases ^a	1	17,350		
	2	43,505		
	3	69,817		
	4	87,533		
	5	96,575		
	6	96,865		
	7	97,156		
	8	97,447		
	9	97,739		
	10	98,033		

(continued)

Table A-3. Summary Results (continued)

ATP Project	Number of Patients			
	Year	Forecast Estimate	95% Confidence Interval	
			High	Low
Universal Donor Organs for Transplantations	1	1,200	1,200	1,200
	2	2,361	2,638	2,084
	3	3,610	4,203	3,020
	4	4,852	5,705	3,968
	5	5,982	6,949	4,883
	6	6,919	7,832	5,726
	7	7,631	8,379	6,464
	8	8,132	8,684	7,082
	9	8,465	8,843	7,579
	10	8,675	8,923	7,964

^aWe did not estimate a model for this project because the company representative gave us a 10-year forecast.