Innovative Response: How the Spinal Marrow Clot May Transform Spinal Fusion Surgery

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Tommaso

ABSTRACT

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Keywords: Innovation, Diffusion, Adoption, Medical Research, vBMA clot

This Teaching Case discusses a scientific research project developed at IRCCS Istituto Ortopedico Rizzoli. The findings describe the process of creating an innovation in spinal fusion surgery using a cell-based therapy based on whole vertebral bone marrow aspirate (vBMA). The purpose is to analyze how this innovation that may impact a significant sector of the medical industry, came into being. And, from this case, we seek to provide insights into how innovation develops and gains diffusion. Given the projected exponential increase of spinal fusions in the next 40 years and high costs of current procedures, vBMA offers an opportunity to transform conventional spinal fusion surgery. In this context, vBMA emerges as a potentially disruptive force, aimed at redefining and revolutionizing conventional spinal fusion surgery practices. It also has the potential to significantly reduce costs while maintaining a high rate in successful patient outcomes, which makes it a game-changer in the medical industry. We discuss the process – from how the idea came about to shifting medical practices and industry resistance – which makes the Case relevant for students of innovation and entrepreneurship. Students will acquaint themselves with key challenges encountered during the process of innovation adoption and the hurdles associated with bringing about disruptive change.

RESUMO

Título da Dissertação:

Autor: Tommaso Barbanti Brodano

Palavras-chave: Inovação, Difusão, Adoção, Investigação médica, coágulo vBMA

Este Caso de Ensino aborda uma investigação científica desenvolvida no IRCCS Istituto Ortopedico Rizzoli. Os resultados descrevem o processo de criação de uma inovação na cirurgia de fusão vertebral utilizando uma terapia celular baseada no aspirado de medula óssea vertebral (vBMA). O objetivo é analisar como surgiu esta inovação que pode ter impacto num sector significativo da indústria médica. E, a partir deste caso, procuramos fornecer uma visão sobre como a inovação surge e ganha difusão. Dado o aumento exponencial projetado de fusões vertebrais nos próximos 40 anos e os elevados custos dos procedimentos actuais, a vBMA oferece uma oportunidade para transformar a cirurgia convencional de fusão vertebral. De facto, neste contexto, a vBMA surge como uma força potencialmente disruptiva, com o objetivo de redefinir e revolucionar as práticas convencionais de cirurgia de fusão da coluna vertebral. Tem também o potencial de reduzir significativamente os custos, mantendo uma elevada taxa de resultados bem sucedidos para os doentes, o que a torna num fator de mudança na indústria médica. Discutimos o processo - desde o surgimento da ideia até à mudança das práticas médicas e à resistência da indústria - o que torna o Caso relevante para os estudantes de inovação e empreendedorismo. Os estudantes irão familiarizar-se com os principais desafios encontrados durante o processo de adoção da inovação e com os obstáculos associados à introdução de mudanças disruptivas.

INTRODUCTION

The spinal column is a fundamental element of the body, serving a variety of functions. It acts as a vital shield for the spinal cord and nerve roots, safeguarding these crucial components of our nervous system. Additionally, it provides a column for attaching ligaments, tendons, and muscles that facilitate movement. Structurally, it lends crucial support to the head, shoulders, and chest, anchoring these vital regions. Moreover, it serves as the connecting link between the upper and lower body, promoting balance and even weight distribution. Remarkably, the spine offers flexibility and mobility in four dimensions, allowing us to bend, twist, and move in various ways. Lastly, bones within the spine contribute to the production of red blood cells and serve as a mineral reservoir that is indispensable for overall health and functionality (Waxenbaum J. et al., 2018).

The spine extends from the pelvis to the skull and is composed of 33 individual bones called vertebrae. These are divided in 4 regions followed by the coccyx. Starting from the top these are the cervical, thoracic, lumbar, and sacrum regions. Cervical vertebrae are divided into upper cervical (C1, or Atlas, is the first support of the cranium and C2, or Axis) and the lower cervical (C3 to C7) (Waxenbaum J. et al., 2018). The thoracic vertebrae increase in size compared to the region above and range through T1 to T12. The rib cage is attached to the vertebrae from T1 to T10, limiting the thoracic spine's movement. The size of the lumbar vertebrae increases even more since these five bones (L1 to L5) bear much of the body's weight and related biomechanical stress. Lastly, the sacrum is made of five more vertebrae (S1 to S5) that fit together into a triangular shape which is located between the hips. The coccyx is also composed of 5 small bones, and it is located right below the sacrum (Waxenbaum J. et al., 2018).

The spinal curves, known as kyphotic and lordotic curves, offer both resilience and flexibility in distributing body weight and axial loads during motion. Movement of the column is also made possible by the intervertebral discs, fibrocartilaginous cushions situated in between vertebrae, which allow extension and flexion of the spine, while protecting the bones and nerves through its shock absorption system (Waxenbaum J. et al., 2018).

From the inception of Dr. Fred H. Albee's bone grafting in 1906 and Dr. Russell A. Hibbs' pioneering work in orthopedic surgery from 1911, spinal fusion has evolved into one of the most frequently conducted orthopedic procedures. Originally addressing instability caused by vertebrae damaged by tuberculosis, the scope of indications for spinal fusion has significantly

expanded over time. Over the past decades, surgical techniques have advanced, allowing spinal fusion to be applied in diverse scenarios, including treatment of traumatic injuries, deformities, primary and secondary tumors, infections, and degenerative spine conditions (Reisener M. J. et al., 2020). There exists a diverse array of fusion techniques, encompassing anterior, lateral, or posterior approaches, as well as interbody fusion options with stand-alone cages or internal fixation. The choice of fusion method depends on the surgical indication, surgeon preferences, and the patient's condition.

The number of surgeries conducted across different fields has been constantly increasing, especially spinal surgery (P. Garcia et al., 2018). For the latter, posterior spinal fusions are essential interventions to treat different spinal diseases. The most common condition requiring spinal fusion is lumbar degenerative disc disease (DDD), which is caused by the stiffening of one or more intervertebral discs (Reisener MJ. et al., 2020). Over time, pedicle fixation systems for spinal stabilization have undergone advancements to incorporate biomechanical principles of spinal stability and incorporate innovations in new technologies and materials. These systems can vary in several aspects, including their means of attachment to the spine, the specific design of pedicle screws (mono- vs. poly-axial), the configuration of the screw-rod connection system (side- vs. top-loading), and the biomaterials employed in the process (Reisener MJ. et al., 2020).

Lumbar interbody fusion with a posterior apparatus saw even wider use for treating degenerative spine diseases after the FDA approval in 1996 for intervertebral fusion cages. Surgeries have risen for degenerative disc diseases where symptoms persist despite nonoperative treatments, for those needing correction in the lumbar lordosis to restore sagittal balance, people suffering from segmental instability and for spinal malformations (Deyo RA. et al., 2003). In the USA alone, 5,000 lumbar interbody fusion cages are being surgically placed per month (Pardhan B. W., et al). Degenerative disc disease impacts the intervertebral discs within the spine. Although it is more prevalent among older adults, it can also manifest in younger individuals. Frequently, age-related alterations at the cellular level can initiate disc degeneration of discs causing gradual decline in structural resilience, flexibility, robustness, shock-absorption capabilities, height, and form. These changes may ultimately contribute to a torn, bulging, or herniated disc.

"Degenerative disc disease"
Source: https://www.spinemedli.com/degenerative-disc-disease/

Spinal fusion involves the use of bone grafts, in addition to synthetic materials, to aid and promote bone fusion. Bone grafts primarily serve to stimulate the healing of bone tissue by providing a scaffold to grow on. Only when new bone is built, can vertebra heal, therefore screws and rod implants can only create temporary stabilization. Autologous bone grafts, or autografts taken from the patient represent the "gold standard" (Tedesco G, 2023) for spinal fusion surgery due to their osteoconductive (stimulating ingrowth of blood vessels), osteoinductive (promoting differentiation of stem cells), and osteogenic (facilitating bone growth) properties. This bone is usually collected by conducting a nerve decompression, where small osteo pieces are removed to alleviate the pressure from the nerves of the spine.

However, disadvantages include pain in the removal site, the duration of surgery, and limited bone availability, especially in the case of multi-level fusion. An alternative to autologous bone is the use of an allogenic bone graft, or allograft (from a donor). Allogenic bone is a highly controlled tissue held in tissue banks, obtained from donor cadavers. Thanks to advanced harvesting techniques, these tissues can be effectively used for surgical purposes. In spinal surgeries, allografts are frozen or freeze-dried before being used to decrease host body's graft rejection. However, there are issues associated with its reduced biological properties, limited osteointegration capacity, lack of vascularization, and limited osteoinductive and osteoconductive abilities (Tedesco G., 2023).

This treatment has been highly efficient, but there still is a high rate of revision surgeries after spinal fusions (ranging from 9% to 45%), mainly due to non-union or infections, or post-surgery cases of pseudoarthrosis (Deyanira C., 2023). This happens due to factors such as age, gender, multilevel fusions, grafts, and the surgical approach. For this reason, several methods,

such as new bone graft materials, cells and growth factors have been tested to improve spinal fusions. Nevertheless, finding processes to establish solid fusion between neighboring segments of the spine continue to pose challenges.

INTERBODY FUSION TECHNIQUE	INDICATIONS	ADVANTAGES	DISADVANTAGES
PLIF Posterior Lumbar Interbody Fusion	Degenerative pathologies including segmental instability, recurrent disc herniation, symptomatic spinal stenosis, pseudarthrosis and deformity	Most common, well-trained surgeons Good posterior visualization and possibility for decompression Good interbody height restoration Option for 360° fusion through single approach	Paraspinal muscle damage and hence prolonged postoperative recovery Aggravated endplate preparation Challenging correction of coronal imbalance and restoration of lumbar lordosis Neural/dural injury
TLIF Transforaminal Lumbar Interbody Fusion	Degenerative pathologies including segmental instability, recurrent disc herniation, symptomatic spinal stenosis, pseudarthrosis and deformity	Sparing posterior ligamentous and reducing iatrogenic paraspinal muscle damage and improved postoperative biomechanical stability Reducing the risk of nerve root and dural injury Option for 360° fusion through single approach	Difficult endplate preparation Limited overall view comparison to conventional bilateral PLIF Challenging correction of coronal imbalance and restoration of lumbar lordosis
LLIF Lateral Lumbar Interbody Fusion	Degenerative pathologies including deformities in combination with a posterolateral fusion, lumbar laterolisthesis	Minimal invasive muscle-splitting approach with potential for faster postoperative mobilization Sufficient deformity correction Endplate preparation Cage size diameter larger in comparison to posterior approaches with good correction of lordosis and height restoration	Not suitable for L5/S1 fusion due to iliac crest bone, severe central canal stenosis, bony lateral recess stenosis and high-grade spondylolisthesis/instability Only for patients without prior retroperitoneal surgery or adverse vascular anatomy Injury of lumbar plexus and iliac vessels at caudal levels with difficulties to control due to approach Neuromonitoring is essential due to transpsoas access

ALIF Anterior Lumbar Interbody Fusion	Strict anterior suitable for L4/5 and L5/S1 disc pathologies as osteochondrosis Oblique technique access to lumbar spine for degenerative disc disease	Efficient anterior discectomy similar to LLIF Cage size diameter larger in comparison to posterior approaches with good correction of lordosis and height restoration Sparing posterior and anterolateral psoas muscle and neural structures	Visceral and severe vascular injuries Retrograde ejaculation Increased approach related risks in patients with prior abdominal surgery or adverse vascular anatomy In cases of high-grade deformity additional posterolateral fusion

"*Overview of interbody fusion techniques and their advantages and disadvantages"*
(Reisener MJ. et al., 2020)

The global orthopedic device market generated $36.3 billion in 2022 and is projected to grow to more than $48 billion in 2028 (48.1), with a CAGR of 4.8% (MarketsandMarkets.com, 2023). The industry invests substantially in research and product development, but disruptive innovations are relatively infrequent. This is because practitioners tend to be conservative and stick to reliable and tested techniques while avoiding seemingly risky innovations; and, alternatively, moving new products though the safety-testing proceedings is a lengthy and arduous process.

"Lateral lumbar interbody fusion cage with integrated modular plate fixation (2-screw-left; 4-screw-right)"
(DenHaese, Gandhi, et al., 2020)

LITERATURE REVIEW

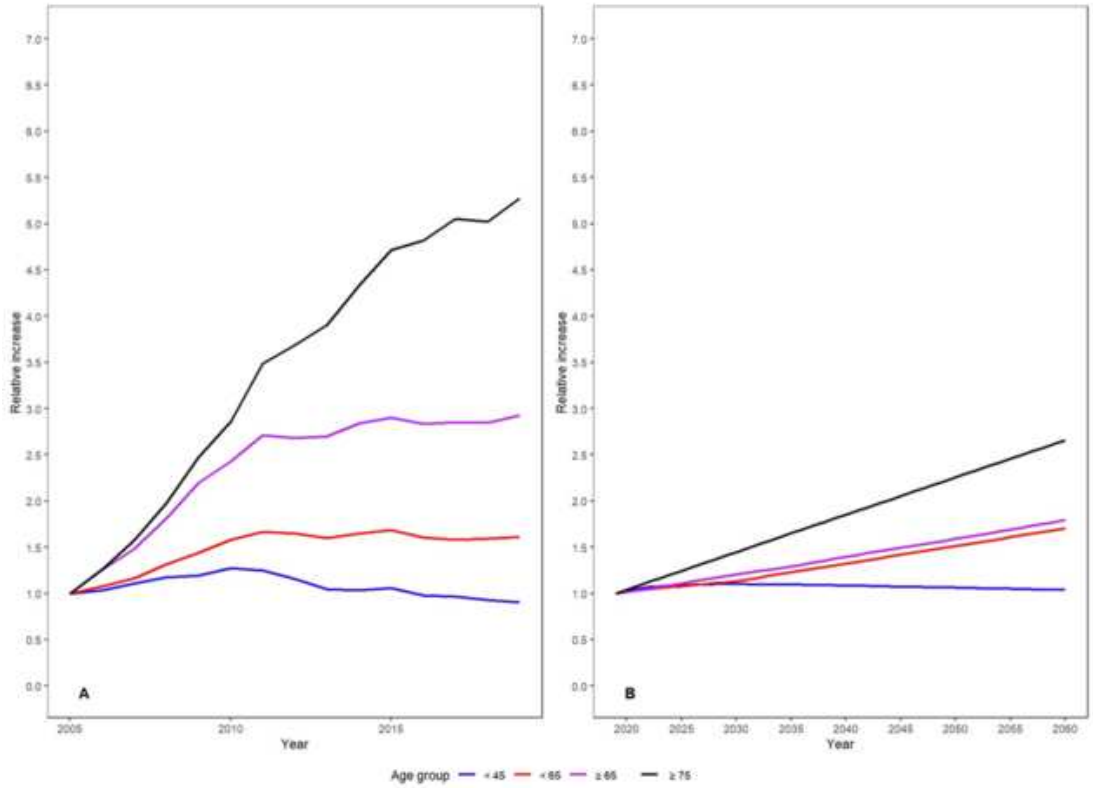
Spinal surgery has mainly relied on spinal fusion for treating degenerative spinal diseases. It is a well-established surgical procedure that has been extensively practiced. According to a study conducted by Heck J. et al. (2023), this treatment has become one of the most expensive medical procedures. Moreover, the study, conducted in Germany, demonstrated that the country's demographic transformation, with low fertility rates, increasing life expectancy and an aging population, will put the healthcare system under severe pressure. Germany was selected because it provides comprehensive and high-quality data on spinal fusion procedures, and also offers free access to medical care. Additionally, the German population will age in the period observed at a rate corresponding to other developed countries. Older generations most affected by degenerative disc diseases, are expected to increase the most: the volume of people older than 75 is projected to grow from 2.7% (1950) to 9.1% (2025) to 14.6% (2050), (Szpalski M. et al., 2003). Germany also has a developed economy with high GDP, making it a meaningful proxy for other industrialized countries experiencing similar trends.

Heck's team observed how spinal fusions in Germany are projected to evolve during the period 2019 to 2060. They analyzed extensive data provided by the Federal Statistical Office through an "autoregressive integrated moving average model on historical procedure rates from 2005 to 2019 in relation to official population projections from 2020 to 2060 chosen to forecast future absolute numbers and incidence rates of this procedure in Germany". During the study, they excluded 2020 and 2021 because data was strongly affected by the impact of COVID on surgeries (Heck J. et al., 2023).

The analysis showed that 595,148 spinal fusions were conducted from 2005 to 2019, with an annual increase from the first to the last year of 115% (21,487 in 2005 to 46,233 in 2019). Relative to annual population growth, the incidence grew considerably: from 26.1 per 100,000 individuals to 55.6 per 100,000 ($p<0.001$). The highest relative increase, as expected, occurred in the category of 75 years and older, with 1.2 spinal fusions more performed on women compared to men (Heck J. et al., 2023).

The projections were based on demographic analyses conducted by Pötzsch O. and Rößger F. (2022), which expected a solid increase in life expectancy in 2060 (89.6 for women and 86.2 for men) and modest birth rates (1.55 children per woman) and immigration (221,000

individuals per year). The study showed a constant projected increase in the number of spinal fusions in the period observed. More specifically, the incidence rate (IR) of these procedures in Germany would rise by 83% from 2019 to 2060, to an expected total of 81,244 in 2060. The large increase in spinal fusions was mainly led by the rising number of people 75 years and older (246% increase in total spinal fusions for women of 75 and more and 296% for men).



(Heck J. et al., 2023)
(A) The historical relative increase in spinal fusion procedures performed from 2005 to 2019 in relation to the numbers of 2005 (per age group)
(B) The estimated relative increase of spinal fusions performed from 2019 to 2060 in relation to the number from 2019 (per age group)

Numerous factors are responsible for the rising rates of spinal fusion procedures. These include deeper understanding of the biomechanics and pathophysiology of the human spine, enhanced diagnostic imaging techniques, broader surgical indications, the development of various instrumentation methods and increased availability of spinal fixation devices, the emergence of minimally invasive surgery (MIS), novel surgical approaches, and innovative alternatives in bone graft materials. Additionally, significant technological advancements, a growing pool of highly trained spine specialists, greater life expectancy, and overall improvement in the safety profile of spinal fusion procedures all contribute to the ongoing upward trend in spinal fusion surgeries. Overall improvement in the safety of these procedures, resulting in lower

complication rates, may also help explain the decrease in reoperation rates (Grotle M. et al., 2019).

Weiss AJ. et al. (2011) found that in 2011 spinal fusions represented the most expensive procedure amongst all surgeries performed in hospitals in the United States. The growing prevalence of spinal fusion surgeries, coupled with expected demographic shifts in developed nations with larger aging populations (a significant portion of whom will undergo spinal fusion procedures), is projected to apply strong pressure on healthcare systems across the globe. This burden will be particularly pronounced in nations experiencing rapid aging, like Germany, stressing human and financial healthcare resources.

Obviously, these projections come with caveats and limitations. For instance, basing extrapolations exclusively on historical data raises the problem of induction that the same patterns may not occur in the future. Technological innovations in this field, although difficult to predict, may potentially have an impact also. For example, if new preventative therapies are introduced, demand for spinal fusions may decrease. However, as stated above, new technologies or procedures tend to take time to proceed from trials to full adoption and commercialization. Therefore, these data are likely to be accurate for the 40 years analyzed (Heck J. et al., 2023).

INNOVATION

An innovation is “an idea, practice or object that is perceived as new by an individual or other unit of adoption” (Rogers E. M., 1983). The perceived originality of the idea for an individual dictates his reaction to it. Innovations can be the result of a market-pull, where the market presents a customer need or problem that will trigger research and development designed to find an innovative solution. Or they may trace to a technology-push (Uriona-Maldonado M., 2010), which entails predicting a future problem that initiates research to find a solution. In this case specifically, technology is defined as a “design for instrumental action that reduces the uncertainty in the cause-effect relationship involved in achieving a desired outcome” (Rogers E. M., 1983). Medical innovations tend to be technological pushes. The foundational knowledge for a technology often originates from research aimed at advancing scientific knowledge rather than solving empirical problems. On the other hand, applied research is based on addressing practical issues. This knowledge is then applied to develop innovations that can

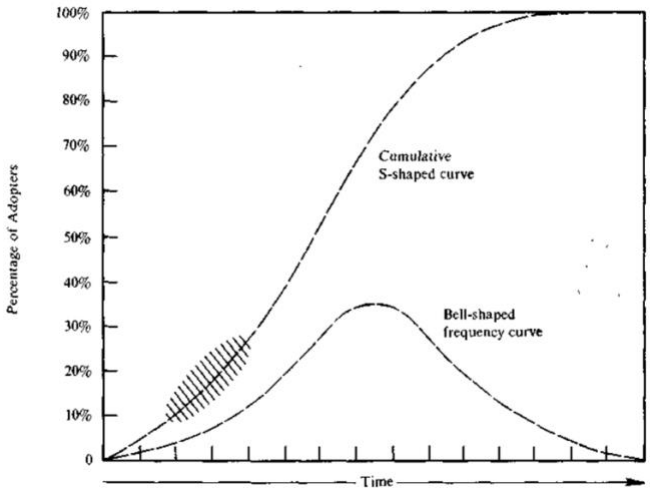
address identified needs or issues. Applied researchers predominantly rely on the findings of basic research.

Research can be defined as successful when it leads to a patent, where the intellectual property rights of the investigator are legally protected by the government for twenty years (European Patent Office, 2023). This safeguards the product during the period in which it is first commercialized. To be granted a patent, the idea must be original and not overlap with any other patented knowledge. Once it is published, the research becomes available to the public. Therefore, patents are useful to diffuse new ideas and discoveries, while at the same time restricting their commercial use. Normally, owners sell licenses to use the research for an initial lump sum payment, followed by royalties, which is a percentage of the sales generated through the work (Rogers E. M. 1983).

The term “disruptive innovation,” introduced by Clayton Christensen (1997), describes how new technologies or business models enter the market and eventually disrupt established industries or products. Christensen states that disruptive innovations typically start by serving niche or underserved markets with products or services that are initially inferior to existing solutions but are more affordable, accessible, or convenient. Over time, performance is improved and gradually captures a larger share of the market, ultimately displacing incumbent technologies or businesses. Disruptive innovation is a significant force shaping how change occurs in industries and proposes that firms must adapt to remain competitive in rapid and dynamic business environments. Schmidt G. M. and Druehl C. T. (2008) frame a disruptive innovation as a new product that does not over-perform an older analog in its primary aspects, but rather functions better regarding a different dimension, which then opens a new market, or introduces a new approach that elevates the quality of the product.

Understanding when a disruptive innovation is introduced into a market is crucial, especially in the short term, because if an incumbent reacts in the medium or longer term, it will likely be too late and may have catastrophic consequences for the business. However, it is especially true that in the short run it is harder to come up with a response since when an innovative product first reaches the market, is likely not to have a disruptive nature (Schmidt G. M. et al., 2008).

Another important factor is the time an innovation takes to be accepted by the members of a social system, defined as rate of adoption. The cumulative frequency of the number of individuals adopting a new idea over time follows an S-shaped distribution. In the beginning a small number of individuals accept the innovation in each period (year or month, depending on the unit of measurement chosen for time). These are early adopters. However, before long the curve begins to steepen as the diffusion spreads to more users. Eventually, the line climbs even more and almost nobody is left-out. Finally, the S-shaped curve arrives at its peak, where diffusion plateaus. Variation usually occurs in the steepness of the curve, which depends on how rapidly the diffusion takes place. Why diffusion of some innovations occurs more rapidly than others is a topic of considerable research (Schmidt G. M. et al., 2008). Another method to show the rate of diffusion is through a bell-shaped curve. The difference lies in the fact the S-curve represents adopters on a cumulative basis, while the bell shows the individuals that adopt each year.



(Rogers E. M., 1983) "*The bell-shaped frequency curve and the S-shaped cumulative curve for an adopter distribution"*

Arguably the pivotal moment of the entire innovation process is the decision to initiate diffusion to potential adopters. There is often pressure to accelerate approval for diffusion due to social need, with public funds potentially supporting the research, or returns on investment remain unrealized until the innovation gains adoption. On the other hand, reputation and credibility of the change agency are sometimes tied to recommending only those innovations that genuinely benefit adopters. When scientists transition from scientific findings to practical applications, caution tends to prevail (Schmidt G. M. et al., 2008).

For medical innovation diffusion, there is concern about “quality control”. This is needed to ensure that:

1. Only innovations with desirable consequences are diffused.
2. Specific innovations are not spread too rapidly.
3. Once adopted, some innovations are not used excessively.

Given potential risks to human life, regulating the diffusion of new medical technologies is entirely justified. Since 1977, the National Institutes of Health has overseen medical innovations through “Consensus Development Conferences”. Consensus development is based on processes whereby biomedical research scientists, practicing physicians, technicians and consumers come together to collectively determine whether a specific medical innovative technology is safe and effective (Lowe C., 1980). The innovation could be a device, drug, or medical procedure and a diverse panel is tasked with addressing questions about the particular innovation. A typical three-day consensus conference commences with a series of research papers that are deliberated upon by expert investigators, users of the technology, and the consumers of such technologies. The panel then formulates a consensus statement, which is presented to the audience on the final day of the conference for their input. Subsequently, the final consensus statement is published by the U.S. Government Printing Office and broadly disseminated to physicians, the mass media, medical journals, and the general public. On occasion, consensus panels have recommended against the use of specific medical or surgical procedures. Therefore, they play a crucial role in regulating the transition of medical innovations from research to practical application (Schmidt G. M. et al., 2008).

Medical innovations undergo clinical trials, which may occur during the commercialization phase of the innovation development process. Clinical trials are structured scientific experiments designed to prospectively assess an innovation's effectiveness, safety, and other critical factors. Within the medical field, clinical trials typically incur costs averaging between $1,000 and $2,000 per patient annually. If a clinical trial involves 100 patients receiving a new drug, the total budget could range from $100,000 to $200,000. In the field of cardiovascular disease therapies, clinical trials frequently entail thousands of patients, hundreds of medical researchers, and costs as high as $100 million (Finkelstein et al., 1981). Thus, the primary objective of clinical trials is to assess the impact of an innovation under real-world conditions, providing the basis for a go/no-go decision regarding diffusion.

FDA PROCESS

A product, device, or methodology, before reaching the market, must go through the FDA Device Development Process, which is a 5-step proceeding that ends up with the approval to be launched.

1. Device discovery and concept:

The FDA categorizes medical devices into 3 classes according to risks they pose, as stated in the Federal Food, Drug and Cosmetic Act, section 513. A device can change its category depending on scientific data analyses. The higher the class, the more controlled devices are. Each class has to go through regulatory controls, which include the 510(k) regulation, which requires evidence that the device is substantially equivalent (SE) to a legally marketed device that is not subject to Premarket Approval:

Class 1 devices only go through "general controls", which ensure their safety and efficiency once they are produced.

Class 2, given their higher potential risk, go through the same general controls, plus other specific controls, mainly regarding labeling requirements.

Class 3 devices are those that maintain patients' lives, are implanted, or have a high risk of injury. Therefore, these devices require proof of safety and effectiveness before receiving approval.

2. Preclinical Research, Prototype:

Medical researchers create a prototype of the device, not for human experimentation at this stage, that is tested under controlled laboratory conditions. The purpose of these trials is to minimize risks of harming the patients, although it is impossible to eliminate these entirely. In medicine, especially in the field of surgery, there is always some risk.

3. Pathway to approval:

The premarket approval is obtained only if valid the safety and effectiveness criteria are met for Class 3 devices or if the device is found not to be substantially equivalent to other Class 2 and 1 devices (510(k) regulation). Moreover, benefits to patients' health must outweigh risks, and there must be statistical evidence that the device will help a large portion of the target population.

4. FDA review:

Once there is data regarding about the device's safety and effectiveness, an application is made to launch the product. This depends on the class of device.

- Humanitarian device exemption

Humanitarian Use Devices offer a benefit to patients affecting fewer than 4,000 individuals. Prior to marketing a Humanitarian Use Device, researchers are required to submit a human device exemption and provide evidence that no comparable legally approved devices are available and that there are no alternative means to introduce a Humanitarian Use Device to the market.

- Premarket Notification or 510(k) – Class 1,2 and 3 Devices

Premarket Notification, commonly referred to as a 510(k), signifies that a Class 2 medical device shares similarities with existing products. To mitigate this, the researcher conducts a comparison between the new device and one or more legally approved devices that are similar.

- Premarket Approval Application – Class 3 Devices

Premarket Approval (PMA) applications are mandatory for Class 3 devices and necessitate inclusion of data from both nonclinical and clinical studies. Throughout the approval process, the FDA conducts inspections of the manufacturing laboratories and facilities responsible for producing the device, ensuring compliance with good manufacturing practices.

5. FDA post-market safety and monitoring:

While premarket clinical trials offer crucial insights into the safety and effectiveness of a device, it's conceivable that new safety concerns may surface once the device becomes available. Consequently, the FDA maintains ongoing surveillance of device performance even after approval. FDA inspections may be scheduled or unannounced. They can be routine checks or prompted by specific issues. The primary objective is to verify that developers are adhering to good manufacturing practices. In cases where standards are not met, the FDA has the authority to suspend a manufacturing facility (FDA, 2018).

A NEW METHOD

As mentioned above, the main substitutes for autografts are bone allografts, but a recent new methodology has been introduced: a cell-based therapy based on whole vertebral bone marrow aspirate (vBMA). vBMA is easily obtained through transpedicular aspiration during spinal procedures (Tedesco G., 2023) but its surgical use is still limited. Issues include not yet established processing procedures and risks of potential dispersion from the implantation site.

Recently however, a research group from the Complex Structure of Surgical Sciences and Technologies in collaboration with the Spine Surgery Unit and the Scientific Direction of IRCCS Istituto Ortopedico Rizzoli of Bologna, Italy, has come up with an innovative solution: the use of a disruptive formulation known as the vBMA clot. This coagulation naturally forms from bone marrow, preserving all the components of the vertebral bone marrow aspirate within a matrix formed by the clot. This three-dimensional matrix (3D) provides unique beneficial effects, facilitating the delivery of mesenchymal stem cells (MSCs) and alpha granules, platelet-specific proteins, cytokines/chemokines, growth factors, coagulation factors and adhesion molecules (Salamanna F. et al., 2023). While donor age, existence of metabolic bone diseases or other intrinsic factors may lead to variations in the biological quality of MSCs within BMA, a study published in 2022 (Salamanna F. et al.) showed that the vBMA can be efficiently used without jeopardizing cell viability, proliferation, and differentiation, even in older patients. Having a clear understanding of the inherent properties, proliferative capabilities and differentiation capacity is fundamental for the eventual future use of vBMA clots personalized tissue engineering and regenerative medicine.

In 2020, the Group described the properties of vBMA clot for the first time, demonstrating that MSCs derived from clotted vBMA possess:
- A higher growth rate compared to MSCs derived from non-clotted vBMA.
- Increased expression of growth factors such as transforming growth factor beta (TGF-β), vascular endothelial growth factor A (VEGF-A), and fibroblast growth factor 2 (FGF2).
- Enhanced differentiating capacity toward the osteogenic phenotype.
- Reduced expression of the genes Pbx1 and Meis3, which are TALE and HOX class genes that negatively regulate the expression program underlying the proliferation, differentiation, and maturation of osteoblasts (Salamanna F. et al., 2023).

These results demonstrated that the vBMA clot has superior biological properties compared to other BMA biological formulations. Considering the increasing prevalence of spinal surgery in elderly patients, the study also assessed the impact of aging and aging-related factors on the biological properties of vBMA clots. The results, published in 2022 (Salamanna F. et al.) demonstrated that the donor's age does not influence the biological and regenerative properties of vBMA clot, such as the expression of growth factors, morphology, vitality, and osteogenic differentiation capacity of resident MSCs, as well as the gene expression of Klotho (an aging

suppressor gene) and the expression of specific genes associated with senescence and aging (IL1β, IL1α, IL6, IL8, TNFα, MCP-1, CCL4, CXCL2). Moreover, utilizing clotted vBMA not only removes the necessity for concentrating and/or purifying vBMA, but also offers an innovative cell therapy strategy for spinal fusion that can enhance the "stability" at the graft site when compared to current methods.

To reinforce these findings with further data, a pilot clinical experiment using clotted vBMA as a biological scaffold in spinal fusions is currently being conducted with 10 patients suffering from degenerative spinal diseases at IRCC Istituto Ortopedico Rizzoli. In addition to the ability to regenerate itself, the research group has identified the following points that make that the vBMA clot a convenient option to tackle all the fundamental obstacles of spinal fusion surgery (Salamanna F., et al., 2022):

1. The vBMA clot serves as a three-dimensional (3D) bioscaffold with osteogenic and osteoinductive properties, housing pluripotent mesenchymal and hematopoietic stem cells that collaborate to stimulate bone formation and regeneration.
2. Within the vBMA clot, the degranulation of platelets results in the release of various biomolecules, including α-granules, platelet-specific proteins, cytokines/chemokines, growth factors, coagulation factors, and adhesion molecules, which have the potential to facilitate early vascularization, crucial element for bone homeostasis, healing, regeneration, and the osseointegration of hardware.
3. Mesenchymal progenitors within the vBMA clot exert an immunomodulatory effect via paracrine mechanisms, thereby regulating inflammation effectively and promoting an optimal transient phase of acute inflammation, which is essential for successful bone healing.
4. The vBMA clot may possess an additional influential aspect through its involvement in the coagulation cascade and the participation of bone marrow mesenchymal stem cells (BMSCs) in the early activation of the innate immune system, which plays a critical role in recognizing and eliminating bacteria (Salamanna F., et al., 2022).

Reporting its findings, the research group stated: “We assume that the ability of vBMA clot to provide a local combined delivery system of stem cells, signaling biomolecules and anti-inflammatory and antibacterial factors enclosed by a matrix molded by the clot represent an advanced and simple strategy to meet the main clinical needs of spinal fusions” (Salamanna F. et al., 2022).

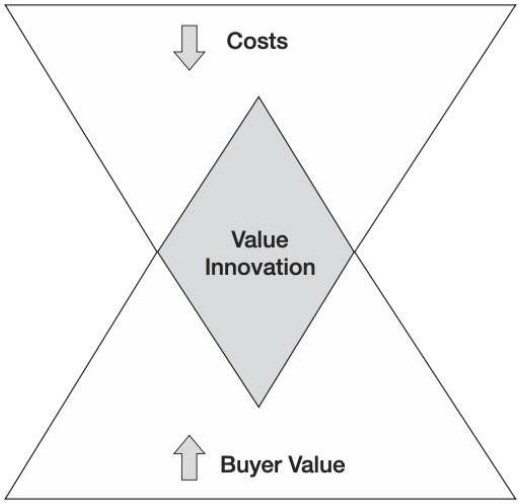
POSSIBILITY TO CREATE A BLUE OCEAN

Kim W. C. and Mauborgne R. (2005) confirmed that no companies remain leaders forever, and the same is true for industries. To be successful, firms must keep innovating and aim strategically to open "Blue Oceans". Blue Ocean strategy requires firms to create a new and uncontested market space that is free of competition. Blue Oceans can also be industries not yet existing or an undiscovered market. In red oceans, on the other hand, competition shrinks margins in crowded markets where firms are in a race to the bottom (White H. C., 1981).

If history is any prognosticator of the future, in fifty years there will likely be many industries that are not present today. This is because industries are dynamic and in constant evolution as new sectors are continuously created (Copernicus and Market Facts, 2001). Therefore, the best unit of measurement is neither the company nor the industry, but instead, according to Kim W. C. and Mauborgne R. (2005), it is the strategic moves that open new market horizons and growth in Blue Oceans. A strategic move is defined as an array of decisions and actions taken at the managerial level, which lead to a major market-opening business possibility.

THE vBMA CLOT EXPERIMENT AT IRCC RIZZOLI

Medical efficacy along with cost advantages are at the core of the vBMA clot as an innovation. Unlike devices currently used in spinal fusion surgeries, associated with high prices, this methodology needs a few mechanical tools and existing medical machinery to realize its benefits. Expensive devices currently in use are substituted by the clot in line with Michael Porter's famous Threat of Substitution (1979) from his five forces. While device manufacturers have focused on offering technologically advanced tools arising out of millions in research, this project has introduced an innovation which, if diffused, may drive the device producers out of the market, disrupting the current industry. For this reason, efforts manufacturers make to compete will become irrelevant if this disruptive method (the vBMA clot as a bioscaffold replacing the intervertebral fusion cage) becomes common practice in an uncontested Blue Ocean market space.



(Kim W. C. and Mauborgne R., 2005), *"The Simultaneous Pursuit of Increasing Buyer Value and Decreasing Costs"*

As shown above, this innovation simultaneously drives value for buyers while decreasing costs. Given the combination of utility and price, value is generated here from these two being in correctly aligned, thereby producing a sustainable long-term strategy.

METHOD OF ANALYSIS – QUALITATIVE RESEARCH METHOD

A qualitative research method using a semi-structured interview was deemed appropriate for this study because it allows for gaining deeper understanding of the experiences, opinions, and perspectives of a key member of the research group developing the vBMA clot procedure. This approach offers flexibility and adaptability for gaining insights through open-ended and follow-up questions.

INTERVIEW DESIGN

To have a deeper understanding of the research conducted at IRCCS Istituto Ortopedico Rizzoli, we interviewed a member of the core team following the project, Dr. Giovanni Barbanti Brodano. An almost 30-year-experienced spine surgeon, he is the main figure representing the Spine Surgery Unit in the team.

The interview was structured in four different sections, we discussed the ideation process of the vBMA scientific research, the journey from the ideation to its execution, the expected diffusion and the potential results. The conversation was composed of 27 questions, mixed between open-end questions and closed-end ones, built according to the Likert scale.

INTERVIEW

IDEATION PROCESS

1. **How was the idea born?**

The process

The project was born because we realized that spinal fusion procedures that require materials such as the autologous bone graft (autograft) and the allogenic bone graft (allograft) have a common problem: they are limited by the quantity of material available. Specifically, allografts that come from bone banks. Therefore, we wanted to create a methodology that didn't have the quantity limit, that had an inexhaustible source.

The vertebral bone marrow aspirate (vBMA) clot is the perfect solution because it can be found already in the patient's body, it doesn't have to be collected externally, especially because each vertebra contains a significant quantity, and the cost to extract is practically null.

The product

To do the vBMA extraction and turn it into clot, very precise actions with specific tools must be done. For this reason, not only a new methodology would be introduced, but also a specific kit made of advanced tools to conduct it effectively. The kit would be composed of a specialized needle for vBMA extraction, a syringe for its aspiration, a container made of a particular material to store the vBMA to make it coagulate, and a few devices.

This is also to remove any chance the approach goes wrong, if the kit is used correctly, according to our methodology, the vBMA will work as a perfect substitute for allograft or autografts in spinal fusions.

2. **Was it from a single person or arose in a collaborative context?**

The idea arose in a collaborative context. It started while we were conducting a research about stem cells with a hematologist from Pisa. We observed stem cells in the bone marrow, while she studied those contained in the blood. The purpose of the study was to test which kind of stem cells between the two types observed were more efficient in building bone cells. According to our normal procedure vBMA, after getting extracted from bone marrow, would be immediately placed into its harvesting station to avoid its coagulation, because it was

thought that once these cells coagulated, they lost their bone-construction capabilities. During an experiment, we forgot to place the vBMA in its harvesting station, the result being that it turned into coagulation, as expected. This time, however, instead of throwing it away, we decided to test it anyway. The results were unprecedented: not only the clot produce bone cells, but it also had a much better result than normal stem cells. From that moment, we decided to focus our studies on the impact of vBMA clot on the production of bone cells.

3. **What was the role of existing scientific papers on vBMA clot in helping move the idea forward?**
    - **Was it useful?**
    - 1 strongly disagree 2 disagree 3 neither agree nor disagree **4 agree** 5 strongly agree

Just like any other scientific research, we relied heavily on the existing literature regarding the vBMA. Multiple studies have been conducted on the stem cells contained, their characteristics and their potential use. However, nobody has considered to use it in spinal fusions. On this field we are innovators, there is no literature we can take advantage of.

4. **Was the idea created to solve a specific problem?**
    - 1 strongly disagree 2 disagree **3 neither agree nor disagree** 4 agree 5 strongly agree

The methodologies that are in use today are totally effective. Surgeons, manufacturing companies and patients are satisfied with them. The purpose of our research is to offer a new methodology that is more efficient, both in terms of materials used and costs. However, I would say that it doesn't offer a solution to a new problem. The problem it is solving was already being solved by the other methods. We are offering an improvement to the available solutions. It eliminates the need to be dependent on external elements to conduct spinal fusions.

5. **To what extent do you consider this a new paradigm in spinal fusion surgery?**
    - 1 strongly disagree 2 disagree 3 neither agree nor disagree **4 agree** 5 strongly agree

6. **To what degree is the idea about solving a scientific problem versus a commercial solution, and a combination thereof?**

- 1 strongly disagree 2 disagree 3 neither agree nor disagree 4 agree 5 strongly agree

The entire experimental result, as I said earlier, came out of a random occurrence. From there, the project was born only to test the potential of vBMA in building bone cells. Therefore, it started as pure scientific research, the commercial side of it came only after we realized that we thanks to our discovery, we opened a new market opportunity. Only then we decided to pursue the commercial side of it.

7. **What is the composition of the development team – ages, backgrounds, etc.**

3 people, one surgeon, one biologist, one

The core team is composed of 3 researchers, a biologist, a clinical researcher and me, a spine surgeon. Around us there are 2 more medical researchers and 2 more surgeons that have helped mainly on the empirical side on the experiments. The ideation, development and data observation has been conducted by the core team.

FROM IDEA TO EXECUTION

8. **How is the idea being progressed from ideation to concrete reality?**

From the point of view of the product development and commercialization, the process we are currently following is predefined by IRCCS (Istitituti di Ricerca e Cura a Carattere Scientifico) as we developed the scientific study with IRCCS Rizzoli. The normative requires us to go through a Technological Innovation Development Office, which will conduct an analysis on the market to look for a corporation that may be interested in working with our project and develop our product. This step has just been completed, as we are now in contact with a medical device manufacturer, but we haven't yet decided how to proceed with them.

From the scientific point of view instead, at the beginning we needed the authorization from the Institute's Ethics Committee to conduct the studies, required to make sure the research would not harm patients or infringe medical regulations. Now we are conducting trial experiments on 10 patients.

9. **Is the process following standard protocols of medical discovery or are there any novel processes involved?**

Only standard protocols. Scientific research involving medical devices must follow standardized practices, otherwise it doesn't get the approval from the Ethical Committee to proceed.

10. Are 10 patients going to be enough for your product testing?

- 1 strongly disagree 2 disagree 3 neither agree nor disagree **4 agree** 5 strongly agree

These 10 patients should be enough to get the data needed. Once the data is collected it is going to be compared with past experiments conducted with allografts and autografts, to see what the performance differences are. Moreover, the normative itself doesn't require for more experiments. However, more data may be required by the company or the potential buyers. So, in that case, we will conduct tests on more patients.

11. What were challenges during the process?

The most complex side of our research were the clinical trials. First, because many patients are not willing to be part of an experimental trial as testers. Understandably, most of them fear being treated with new uncertified methods, they'd rather undergo classical procedures. Second, clinical trials are hard to program according to scientific research requirements. For example, a patient under analysis for scientific testing, may be programmed to be operated on in the night by a specific surgeon who is conducting the test but may end up having surgery earlier due to unexpected emergency problems, with a surgeon that is not involved in the research. That way we lose a patient under observation for our research. Same thing happens with blood samples that must be brought to the lab.

If someone doesn't take care of them, then they get lost. For this reason, we decided to hire a specific clinical researcher that would take care of these small but fundamental details to proceed with our research. Another issue was in the post-surgery, once the patient goes back home, we need to make sure the stem cells are being beneficial to the reconstruction of the bone, so we need to see him after a few months. But he may be on the other side of the country. Every case has its different story, then it becomes tricky to find solutions.

12. What challenges are there going to be in the future?

From the scientific research point of view, most of the challenges have already been overcome. For what concerns the commercial side of it, there will be most likely challenges with the

regulations, as they change in different geographical areas. Therefore we may have to create a slightly different product to be accepted in different regulations.

DIFFUSION

13. When is it going to be diffused?

Hard to say. Going through all the steps to be accepted by Health Care Institutions can be a lengthy process. We want to start its diffusion once we get the patent for the kit and we have a company ready to produce it. We hope this happens within the next 2 years.

14. Don't you risk having it copied by publishing it in the articles?

- 1 strongly disagree 2 disagree **3 neither agree nor disagree** 4 agree 5 strongly agree

We do, a little bit. However, when describing our research, we made sure not to give away the key elements in the methodology. We explained our results, but not how we got there, or at least not every step. This is why many people are contacting us with questions regarding the missing elements, but we are not planning to share it for now.

15. What is the diffusion process going to look like?

First a scientific diffusion is going to be needed. Communication at national and international medical meetings is going to be crucial in the beginning. This is how our innovation will get acknowledged in the market. The second step, essential for the commercialization of the product, is going to be an efficient marketing activity done by the manufacturer through its product specialists. They are key in the diffusion of our product in the hospitals.

16. Do you think everyone will adopt it, making it the common methodology?

- 1 strongly disagree **2 disagree** 3 neither agree nor disagree 4 agree 5 strongly agree

I think it is going to be an alternative to the main methodology. It will be used when the autograft or allografts won't be available or will be too expensive to be used. I think it's hard that our methodology will substitute completely what is out there now. It really depends on the cases. To give you an example, the Istituto Ortopedico Rizzoli has its own bone bank in the hospital, therefore its costs to retrieve an allograft are much lower than Hospital of Treviso for

example, which has to buy it from Rizzoli to use it, as that is the closest bone bank. Therefore, for Rizzoli, the cost of an allogenous bone graft may be equal or even lower than the product we are developing. For an Asian hospital in the middle of nowhere on the other hand, retrieving an allograft may be extremely lengthy and costly, so it may be more convenient to adopt our method from the beginning as the primary solution.

17. Will the innovation be driven by individual surgeons who are converts, hospitals, insurance companies, healthcare systems?

Diffusion will be led by companies that produce the kit, based on its marketing. This is how the medical devices industry usually works. As I stated earlier, the process starts in important medical gatherings where innovations are introduced to the market by researchers. In these situations, we will have to show how effective the results of our studies are. But then it's all about the performance of the marketing of the manufacturer. Normally it would be represented by product specialists that have the role to approach hospitals and surgeons and convince them to use our kit.

18. Do you think the adoption cumulative rate will follow an s-shaped curve?

- 1 strongly disagree **2 disagree** 3 neither agree nor disagree 4 agree 5 strongly agree

It will take time to diffuse, there will be a peak, but it will take time. It will slowly increase at the beginning, when it will become more famous, it will have an exponential increase, reaching a final plateau. I believe the initial adoption will not spread quickly. Once the first teams realize that our methodology is effective, the word will go around, and more hospitals will get convinced to adopt it.

19. What issues do you anticipate that will cause other surgeons to decide not to accept it?

I feel that if the methodology won't be adopted will be mainly due to the efficiency of the methods that are already in use. It really depends on case to case, the game changer is the accessibility to bone banks and synthetic products of institutes. If they are easily retrievable and at a low cost, there won't be an incentive to switch to our methodology. If however, bone banks are located in an inconvenient position for a specific hospital, our product could really make a difference. The issue also lies in the fact that our procedure is a new methodology to solve a problem that is currently already being solved, it simply does it in an innovative, cost-

reducing way. Our advantage is mainly based on the fact that with our approach we erase the quantity limit related to the availability of allografts.

20. **Do you think the companies that manufacture the devices for spinal surgery will fight against the introduction of this method?**
    - 1 strongly disagree 2 disagree 3 neither agree nor disagree 4 agree **5 strongly agree**

Yes, absolutely. At the end of the day, the medical devices are sold in a marketplace that works just like any other. There are competitors that fight to gain a dominant position and will do anything they can to prevent the entry of a new player. There's also to consider that our methodology is simply duplicable in-house. Therefore, a consistent risk is that a major device manufacturer launches a similar or even better version of our kit.

RESULTS

21. **Do you think it will disrupt the industry (create a Blue Ocean)? Over what time frame?**
    - 1 strongly disagree **2 disagree** 3 neither agree nor disagree 4 agree 5 strongly agree

As I said earlier, I don't think it will disrupt the industry. But if it does, it will take time. My guess is 10 years possibly.

22. **What are the key factors that will govern commercialization of the product?**

Marketing conducted by the manufacturing company is crucial. Naturally you must have a product that works and is beneficial for the patient as a basis. In our case, given that our product is not that disruptive, the manufacturer's marketing plays a central role in its success. A fundamental aspect of the product development is its pricing: to have an impact on the market, the price must be as low as possible. This is because during surgeries, materials and products that are not costly get used easily, without second thought, while expensive tools are only used if really necessary. Most of medical devices used for spinal fusion are expensive, if we're able to come up with a cheap solution, we'll have higher chance to convince hospitals to adopt our kit.

23. **How will the Founders, the Institute, etc., be compensated as the procedure takes root and becomes the norm?**

This is a big issue that we face. These kinds of situations are regulated by norms that have recently changed. Before they changed, any scientific research conducted inside an IRCCS was property of the IRCCS itself, and the researchers would only benefit from the royalties resulting from the project's sales. These royalties would be different from researcher to researcher according to their contribution to the project. Back then, scientific research could not even be conducted outside of an IRCCS. The advantage of developing inside an IRCCS was the fact that it would provide all the funds required for the costs of the patent and the manufacturing of the product, so researchers would have to bear no expenses.

Nowadays, researchers are allowed to develop their scientific research outside of an IRCCS, with the advantage being that they would benefit of all the profits coming from it but would also take care of all the costs.

Personally, I believe in this project, and I would rather follow the path to develop it outside of an IRCCS, however not everyone agrees. Moreover, the Scientific Director of Research of the Institute has recently joined the team, therefore there would be a conflict of interests if we end up conducting the research outside of the IRCCS.

24. **Do you think vBMA will completely eradicate the use of other tools for spinal fusions?**
    - **1 strongly disagree** 2 disagree 3 neither agree nor disagree 4 agree 5 strongly agree

Absolutely not, I hope so, but I think it would be a miracle. Especially in the short term.

25. **Considering the lower costs of this method compared to using the current devices, will its introduction affect the price of the surgery for the end customer?**
    - 1 strongly disagree 2 disagree 3 neither agree nor disagree **4 agree** 5 strongly agree

Yes, I think so. Especially in a country like Italy, where health care is a public commodity, and the payment of surgeries is reimbursed by the State. In this case, if we are able to provide a

product that is equally (or even more) efficient compared to the ones in use in terms of success rate, but bears a lower cost, the State may incentivize hospitals to adopt our methodology to end up with a lower final price, which corresponds with a lower reimbursement that comes from public taxes.

26. What is the probability of success of the new methodology?

This is a complex question. In my opinion, the probability of success of the scientific research is quite high. The results are there, they are scientifically proven. We are already using it with our patients. However, going from there to the commercialization of the product may be a rough path. Innovative products are continuously introduced. Most of the times, in the beginning they have the numbers and potential to change the entire industry, but then for different factors they end up in failure.

27. What is your scenario planning for adoption? What issues do you anticipate?

It is hard to say. At the end of the day, the medical device industry is a marketplace, just like any other. If a company is better at selling or has a stronger marketing or even "buys" surgeons to use their product, they end up being more successful. As I said, not necessarily the most advanced product is the one which wins in the market, there are many other factors that come into play. Unless you develop something that really changes the industry, which is not our case.

INTERVIEW ANALYSIS

In the expert interview, we discussed the ideation process behind the innovative spinal fusion procedure involving vertebral bone marrow aspirate (vBMA) clot. The project emerged from a collaborative stem cell research context, offering an innovative solution to the limitations of existing spinal fusion methods. Existing scientific literature did not contribute significantly to the idea, as it was a pioneering application. The transition from scientific research to a commercial pursuit occurred after studying the market potential. Challenges in clinical trials and potential future regulatory hurdles were also discussed.

The diffusion strategy involves scientific presentations and marketing by the manufacturer, with adoption expected to vary based on hospital circumstances. Success may depend on effective marketing, competitive pricing, and intellectual property regulations. Ultimately, the new methodology is not anticipated to disrupt the industry entirely, but it may take around a decade to gain wider acceptance.

SOURCES AND LIMITATIONS

This Teaching Case was based on primary and secondary data. Primary data was obtained through the interview conducted with the expert who is a key individual conducting the research project to perfect the vBMA clot in spinal fusions. Secondary data was found on the internet, mainly from important scientific and medical journals. Although the individual interview enabled us to get insightful information about the scientific research, data available on the internet was limited. Moreover, the project is still at an early stage and far from being launched into the market. For this reason, the research group was less disposed to disclosing sensitive or proprietary information. However, the information obtained through primary and secondary data was enough to have a clear understanding of the research and its future steps.

In addition to qualitative answers, we included some responses with a Likert scale, so future researchers might compare how our expert responded with other opinions from stakeholders related to the project. We acknowledge that time constraints prevented us from speaking with other individuals associated with the project or with people who might be skeptical of the vBMA methodology.

CASE OVERVIEW

With this Teaching Case, students are able to analyze innovation and entrepreneurship in the context of a field of scientific research. The project conducted at IRCCS Istituto Ortopedico Rizzoli is a significant initiative with disruptive potential that can transform an important surgical domain.

This Case is an example of an innovation that resulted from a technology-push. As described by the expert, the research started from the result of a random experiment, which gave interesting insights that were further developed. This explains that there was not clear demand from the market for a new methodology. However, starting from a random experiment, the project turned into an innovation that has transformative potential and which could open up a Blue Ocean of new uncontested market.

We also see how scientific research comes before market research and the diffusion of an innovation. In this case we have a glimpse at the process of scientific discovery from ideation

to the development of the methodology, and then the initial moves towards commercialization. We conclude with a forecast of what its diffusion could be.

TEACHING OBJECTIVES

This Case is designed for students to familiarize themselves with the topic of scientific innovations and the dynamics that lead towards commercialization and diffusion in the market. The case aims at enriching management theory concerning innovations and their diffusion.

From an entrepreneurship point of view, this case is useful for understanding how a disruptive innovation has the potential to open new undisputed markets but at the same time may fail to do so and will instead enter the existing market as an alternative solution. As was argued, specifically for medical devices, marketing is crucial for the success of an innovation when entering the market and, because of sunk costs and other factors, a disruptive procedure might not move from being a niche product into the mainstream.

TEACHING QUESTIONS

1. What difficulties are associated with launching a new medical device? What factors are key to achieve a successful outcome commercially?
2. What are the barriers that may impede the vBMA clot methodology getting to market?
3. Do you think the vBMA clot methodology has a competitive advantage? Apply the VRIN framework to describe it.
4. An innovation may be described as a market-pull or a technology-push, what is the difference? What kind of innovation is the vBMA clot methodology? Why?
5. Based on forecasts of spinal fusions in the future, do you think there will be increasing demand for the vBMA methodology? Why?
6. When is an innovation disruptive? How is the vBMA illustrative of Christensen's notion of Disruptive Innovation?
7. How did the innovation come into being? What role did the surprise factor play?
8. Where would you place the vBMA along the innovation S-curve?

TEACHING QUESTIONS AND ANSWERS

1. **What difficulties are associated with launching a new medical device? What factors are key to achieving a successful outcome commercially?**

Various factors must be taken into consideration including getting through FDA controls, which vary according to the purpose of the device and the risks attached. Once approved the innovation is ready to go to market. However, few new devices achieve successful commercialization. If it is an unprecedented revolutionary technology and has been marketed effectively, this is a surer pathway to commercialization. Scientific innovations must gain a competitive advantage in the marketplace, which, at an early stage, is obtained through marketing.

2. **What are the barriers that may impede the vBMA clot methodology getting to market?**

The vBMA clot methodology is still at the clinical experimentation stage. It has received approval from the Ethical Committee to proceed, but it is still far from ready. As stated in the previous question, the first barrier is going through the controls of the EMA, the European equivalent of the FDA. If approved, marketing is key for diffusion and success. Moreover, effective procedures for spinal fusions are already in place at hospitals globally, so the challenge for this innovation is to be positioned not as a simple substitute, but rather as a better option to what is currently in use.

3. **Do you think the vBMA clot methodology has a competitive advantage? Apply the VRIN framework to describe it.**

The vBMA clot methodology solves a problem that is already effectively being addressed by other procedures. The risk here is whether it can become a substitute for other players in the market. However, the innovation has two main characteristics that make it unique: its low cost and its unlimited availability. This is what has the potential to give it a competitive advantage. To assess this we might apply the VRIN framework used to assess the competitive advantage of a firm. Thus, we can ask how the product might be considered valuable, rare, inimitable, and non-substitutable. We can examine the VRIN criteria using two key dimensions of the product.

1. Low cost:
    - The low cost is valuable. In an industry where medical devices tend to be highly expensive, coming up with a cheaper solution may make a difference. This is particularly relevant for spinal fusions which are one of the costliest procedures.

- Given that no other competitor is offering a cheap device for spinal fusion, the low price of the new procedure can be defined a rare aspect.
- Other companies in the market offer products that require expensive manufacturing and shipment. On the other hand, this methodology is based on using biological elements (vBMA clot) that are extracted directly from the patient's body with the help of a basic kit, which has low cost of production. For this reason, other companies cannot offer their tools at the same or lower price.
- The low price is inimitable and it is also non-substitutable by any other product in the market.

Final assessment: given VRIN attributes, the vBMA clot may be taken to have a competitive advantage.

2. Unlimited availability:
    - Unlimited availability is definitely valuable, especially considering the exponential increase in spinal fusions forecast for the future.
    - Companies are offering tools for the other available methodologies. Although these may be produced on a large scale, procurement issues remain. For this reason, the vBMA clot availability aspect is rare.
    - Unlimited availability is also the result of using biological elements extracted directly from the patient's body. No manufacturer can produce devices using similar materials. Therefore, this is an inimitable aspect.
    - Methodologies that are already in use are reliable and effective. Demand for spinal fusions is increasing, but as of now supply is satisfying that demand. For this reason, the unlimited availability aspect is substitutable.

Final assessment: given that unlimited availability is valuable, rare, inimitable, but substitutable, this aspect can be considered not immune to competitive challenges.

4. An innovation may be described as a market-pull or a technology-push, what is the difference? What kind of innovation is the vBMA clot methodology? Why?

Market pull and technology push represent two distinct approaches to innovation. Market pull is driven by identifying specific market needs, with product development responding to customer requirements. In contrast, technology push starts with a new technology or scientific

discovery, and then explores its potential applications and markets. Market pull is typically less risky, as it responds to existing demand, while technology push carries higher risks, introducing new technologies and convincing the market of their value. Like many medical innovations, the vBMA clot procedure is the result of a technology push, which resulted from a random experimental result in the lab. Researchers accidentally discovered the potential of coagulated vBMA. After further testing, they decided to develop and consequently patent the new methodology. They agreed to launch it in the market along with the minimal kit needed to ensure a successful outcome in spinal fusion.

5. **Based on forecasts of spinal fusions in the future, do you think there will be increasing demand for the vBMA methodology? Why?**

As the rate of spinal fusions is expected to rise exponentially, the cost of these surgeries will place a heavy burden on healthcare globally, both for private and public systems. Since avoiding spinal fusions is not an option, finding cheaper ways to execute will be key. This is how the vBMA clot procedure can become a central player in the market. It addresses a market need through its lower price, and immediate, unlimited availability. Therefore, it is expected that the demand for this methodology will increase.

6. **When is an innovation disruptive? How is the vBMA illustrative of Christensen's notion of Disruptive Innovation?**

According to Christensen, disruptive innovations often begin by supplying niche or overlooked markets, offering products or services that may initially be of lower quality compared to existing solutions but are more cost-effective, accessible, or convenient. After some time, performance improves or gets noticed and attracts a larger share of the market, with the result of bringing about disruptive change.

The vBMA clot methodology has the potential to be a disruptive innovation, as it is designed to satisfy an existing need by offering a cheaper and more convenient option. There is the barrier of existing substitutes, but if marketing is effective and the innovation is noticed in the market, in time it may diffuse and become the market leader. It may even open a new Blue Ocean of uncontested market space.

7. **How did the innovation come into being? What role did the surprise factor play?**

The scientific research started from a random discovery in the lab during an experiment on the ability of the vBMA to generate bone cells through its stem cells. Normally, once extracted, the vBMA is kept in its liquid state and put into its harvesting station to create stem cells. However, if the vBMA clot is not placed in the station right after extraction, it coagulates. Once turned into this state, it was believed that it would lose its bone creation abilities. However, even though a vBMA batch turned into a clot, researchers decided to study its harvesting performance anyway, with unprecedented results. From there, the entire scientific research shifted to analysis of the vBMA clot. This illustrates the factor of surprise and how innovative solutions sometimes come about through lucky accidents.

8. Where would you place the vBMA along the innovation S-curve?

The innovation S-curve is a framework used to describe evolution of an innovation from its inception to diffusion. Considering that the vBMA clot methodology has not yet reached the market, it is still at the earliest stage of the S-curve. It is likely that it is going to take some time before gaining traction in the market which is the S-curve's inflection point. This is because the vBMA clot enters as a substitute to already existing methodologies that are effectively solving the same need. First it must be accepted as a reliable method by the early adopters. In an optimistic forecast, after some time, once it gets widely known in the industry, it will have a higher diffusion rate, following the S-shaped curve.

CONCLUSION

Scientific research has no limits. However, the journey from an innovative scientific finding into the market is never a linear one. As a matter of fact, discoveries can have different impacts on the scientific field and the commercial marketplace. The results from the interview highlighted that a scientific discovery which may be disruptive for medicine does not necessarily translate into commercial success. These types of products tend to face significant hurdles before reaching the market, and even when they do, it is hard to create diffusion. As mentioned, only the most disruptive technologies will definitely have an impact on the market. On the other hand, this is not a sufficient condition to ensure commercial success. Innovative products are introduced into the medical sphere, but only those with an effective marketing strategy gain traction.

Ultimately, despite compelling scientific aspects, it is difficult to predict the full impact of vBMA clot for spinal fusion surgery. As discussed above, this is an innovation that ticks all the boxes for a potential Blue Ocean. However, existing surgical techniques are an impediment to adoption despite the obvious benefits. For this reason, we cannot say whether surgeons nation-wide and then globally, will decide to adopt the innovative approach created by IRCCS Rizzoli. Moreover, the medical industry has a tendency to be resistant to change and reluctant to embrace new products and procedures.

Subsequent research should include more diverse perspectives of people both internal to the project and external stakeholders. In addition, surveys and questionnaires within the industry could better help forecast diffusion of the methodology and its impact on the spinal fusion medical device market.

BIBLIOGRAPHY

1. Waxenbaum J., Futterman B., (2018), "*Anatomy, Back, Intervertebral Discs"*, InStatPearl [Internet], StatPearlPublishing, available at https://www.ncbi.nlm.nih.gov/books/NBK470583/
2. Heck V. J. MD, Klug K. Msc et al., (2023), "*Projections from Surgical Use Models in Germany Suggest a Rising Number of Spinal Fusions in Patients 75 Years and Older Will Challenge Healthcare Systems Worldwide*", Clinical Orthopsedics and Related Research, 00:1-10
3. Garcia P, Domnick C, Lodde G, Raschke M., (2018), "*Operative treatment in orthopaedic surgery: are more operations carried out in Germany?"* [in German]. Unfallchirurg.;121:20-29.
4. Reisener MJ, Pumberger M, Shue J, Girardi FP, Hughes AP. (2020) "*Trends in lumbar spinal fusion-a literature review.*" J Spine Surg.; 6:752-761.
5. Deyo RA., Nachemson A., Mirza SK., (2004), "*Spinal-fusion Surgery – the case for restraint"*, N Engl J Med, 350:722-726
6. Tedesco G., (2023), *"Use of Clotted Vertebral Bone Marrow as Autologous Cellular Therapy and Multifunctional Scaffold for Spinal Fusion - Prospective Randomized Study*" [in Italian], More for Spine, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy
7. Pradhan B. B., Wang J. C., "*Complications of interbody fusion cages"*, UCLA School of Medicine, Los Angeles, CA, USA
8. (2023), "*Orthopedic Devices Market by Product, Braces, Application, End User & Region – Global Forecast to 2028"*, Orthopedic Devices Market, MarketsandMakrets.com [Internet], available at https://www.marketsandmarkets.com/Market-Reports/orthopedic-device-280.html#:~:text=The%20global%20orthopedic%20devices%20market,4.8%25%20from%202022%20to%202028
9. Szpalski M., Gunzburg R., Melot C., Aebi M., (2003), "*The aging population: a growing concern for spine care in the twenty-first century"*, Eur Spine J.; 12 (Suppl 2): S81-83

10. Pötsch O., Rößger F., (2022), "*Demographic analyses, methods and projections, births and deaths: Germany's population by 2060 – results of the 13th coordinated population projection"*, Federal Statistical Office of Germany
11. Weiss AJ., Elixhausera A., Andrews RM., (2011), "*Characteristics of operating room procedures in U.S. hospitals"*, HCUP statistical brief #170
12. Schmidt G. M., Druehl C. T., (2008), "*When Is a Disruptive Innovation Disruptive?",* The Journal of Product Innovation Management, 25:347-369
13. Uriona-Maldonado M., Coelho de Souza L. L., Varvakis G., (2010), *"Focus on practice service in the Brazilian electric energy sector",* Serv Bus 4, 77-88
14. Deyanire C., Sartori M., Tedesco G., Gasbarrini A., Giavaresi G., Salamanna F., (2023), "*Vertebral Bone Marrow Clot towards the Routine Clinical Scenario in Spine Surgeries: What about the Antimicrobial Properties?"*, International Journal of Molecular Sciences
15. Salamanna F., Deyanira C., Borsari V., Pagani S., Sartori M., Tschon M., Griffoni C., Giavaresi G., Tedesco G., Barbanti Brodano G., Gasbarrini A., Fini M., (2023) "*Gender-Specific Differences in Human Vertebral Bone Marrow Clot"*, International Journal of Molecular Sciences
16. Rogers E. M., (1983), "*Diffusion of Innovations*", The Free Press, A division of Mamillan Publishing Co., Inc., Third Edition
17. Christensen C., (1997), "*The Innovator's Dilemma: when new technologies cause great firms to fail"*, Harvard Business Review Press
18. Reisener M. J., Pumberger M., Shue J., Girardi F. P., Hughes A. P., (2020), "*Trends in lumbar spinal fusion – a literature review"*, Review Article on Postoperative Spinal Implant Infection, Department of Orthopedic Surgery, Hospital for Special Surgery, New York, NY, USA
19. Grotle M., Småstuen M. C., Fjeld O., (2019), "*Lumbar spine surgery across 15 years: trends, complications and reoperations in a longitudinal observational stuy from Norway"*, BMJ Open, 9:e028743
20. Lowe, Charles U. (1980), "*The Consensus Development Programme: Technology Assessment at the National In- stitute of Health*", British Medical Journal, 1583-1584.
21. Finkelstein, Stan N., et al (1981), "*Biomedical Innovation: The Challenge and the Process",* Cambridge, Massachusetts Institute of Technology, Sloan School of Management, Report. MR(E)

22. FDA, (2018), "*The Device Development Process"*, FDA US Food and Drug Administration, [Internet], available at: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/device-development-process
23. Kim W. C., Mauborgne R., (2005), "*Blue Ocean Strategy – How to create Uncontested Market Space and Make the Competition Irrelevant"*, Harvard Business School Press, Boston, Massachusetts, USA
24. White H. C., (1981), "*Where do Markets come from?",* American Journal of Sociology, 87, 517 – 547
25. Copernicus and Market Facts, (2001), "*The Commodization of Brands and its Implication for Marketers"*, Auburndale, MA: Copernicus Marketing Consulting