SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

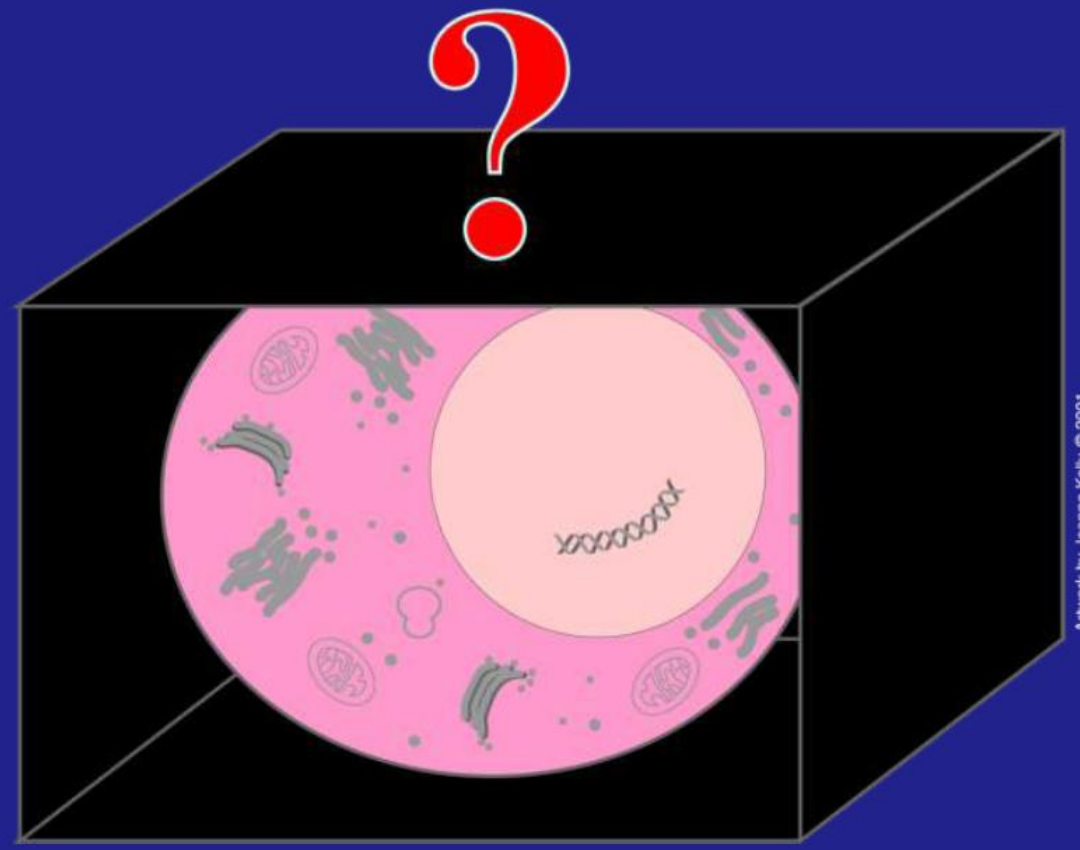
Centro Congressi Unione Industriali
TORINO 11-13 MAGGIO 2023

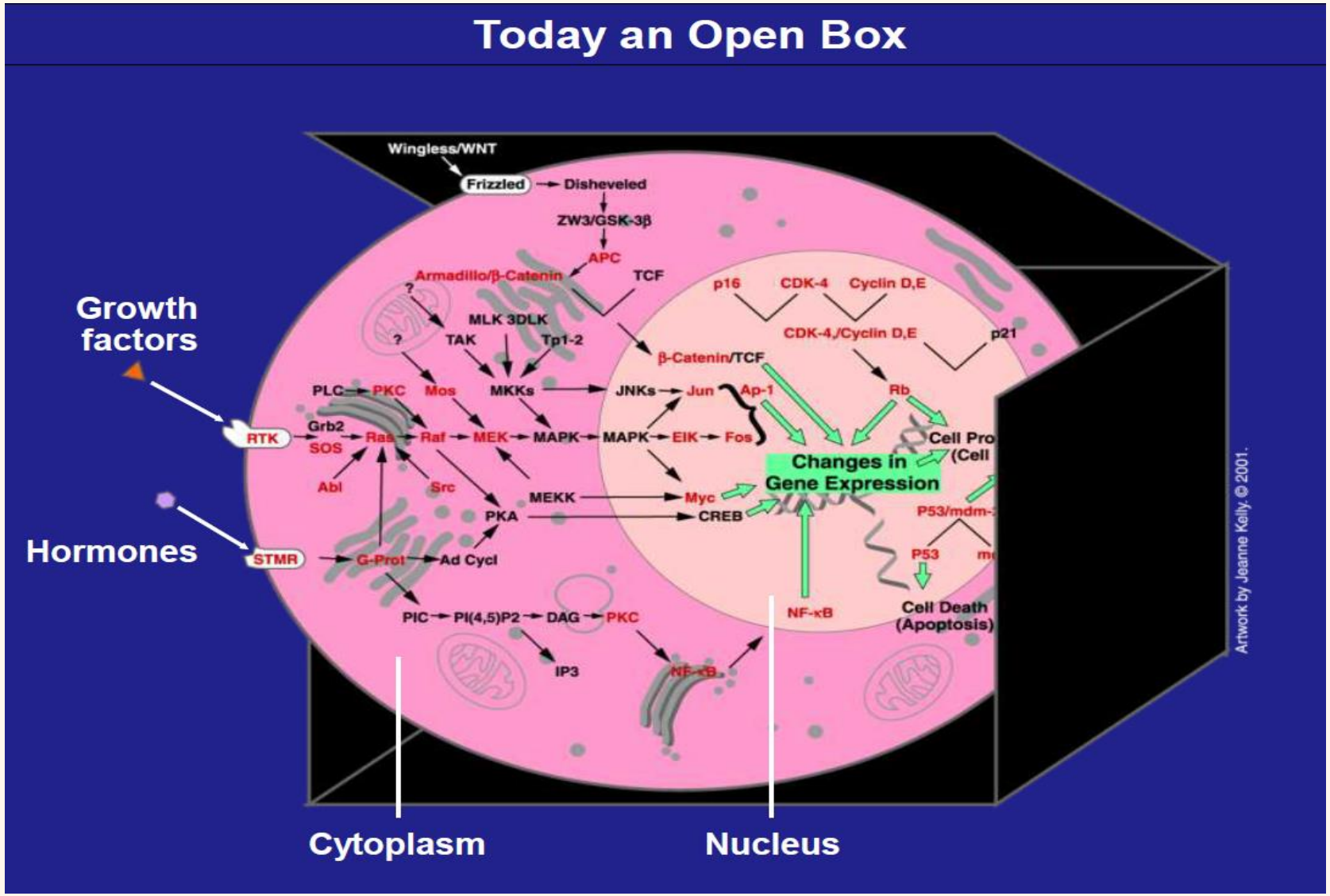
Prof. Antonio Giordano

The Power of Virtual Reality to Personalize Recovery: Lessons from the Clinic and the Sports World

Prof. Antonio Giordano, worked in the Cold Spring Harbor laboratories directed by Nobel Prize winner James Watson.

Once a Molecular Black Box




Today an Open Box
Growth factors
Hormones
Wingless/WNT
Frizzled
Disheveled
ZW3/GSK-3β
APC
Armadillo/β-Catenin
TCF
?
MLK 3DLK
TAK
Tp1-2
β-Catenin/TCF
PLC
PKC
Mos
MKKs
JNKs
Jun
Ap-1
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
EIK
Fos
RTK
Abl
Src
MEKK
Myc
PKA
CREB
STMR
G-Prot
Ad Cycl
PIC
PI(4,5)P2
DAG
PKC
IP3
NF-κB
p16
CDK-4
Cyclin D,E
CDK-4,/Cyclin D,E
p21
Rb
Changes in Gene Expression
P53
Cell Death (Apoptosis)
Cytoplasm
Nucleus
Artwork by Jeanne Kelly. © 2001.

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The Power of Virtual Reality

DEFINITION

- Virtual Reality is the use of computer modeling and simulation that enables a person to interact with an artificial three-dimensional (3-D) visual or other sensory environment;
- Via seeing, hearing, smelling and feeling;
- Common Features in todays world;
- Virtual Reality will have some impact in almost every field in the near future.

WHY VIRTUAL REALITY

- Virtual reality is adopted by military, aviation, sports like golf etc. as training ground in highly realistic manner.
- In military, soldiers can diffuse a bomb without any real world risks.
- In Medicine;
  Earlier: Dissection and study using plastic models;
  Now: Virtual Patients and Virtual Histology
- Can help relieve patient anxiety toward a host of medical scenarios.

With the passage of time & technological progress made by computer technology, it has become ever present in the lives of majority of people

VIRTUAL REALITY is one of them!

- A way for humans to visualize, interact and manipulate with computers
- Advanced form of “human-computer” interaction in naturalistic fashion
- Thomas A. Furness is the grand father of VR

- Virtual reality is a generated, interactive simulation that maps the real environment by affecting human senses and shows all activity in real **time & speed**;
- Stimulates the patient's senses to create an illusion of reality;
- To achieve the goal of realism for the patient which is an incorporation of **perception & cognition**;
- Emulates learning process in the real world, while allowing the addition of extrinsic feedback & increasing the **frequency, duration & intensity** of an exercise.

- Virtual environments can present combinations of stimuli that are not found in the natural world and researchers can execute changes in the environment that would not be possible physically

- VR might be used to decouple visual and vestibular sensation, revealing the roles of separate brain systems that are usually enlisted simultaneously → for example, postural responses may reflect input from visual perception more than from motion perception, or vice versa

THERAPEUTIC APPLICATIONS

- **Neuro-rehabilitation applications** → balance disorders and their underlying multisensory integration mechanisms, and recovery of function;
- VR simulations can be highly engaging, which provides crucial **motivation for rehabilitative applications** that require consistent, repetitive practice;
- The tracking systems used in VR provide an **excellent tool for recording** and following minute changes and improvements over time;
- Immersive multimodal VRs that link head, hand and body movement to changes in visual and auditory stimuli have proven useful for the **recovery of motor function and postural stability.**

THERAPEUTIC APPLICATIONS CONTD..

- **Pain remediation** → Virtual environments provide perceptual representations of one's body and the world that can shift the patient's attention and slightly alter the perceived properties of pain;

- **Psychiatric disorders** → VR treatment has been applied to a range of disorders, including fear conditioning, anxiety disorders and brain damage.

VIRTUAL REALITY USE IN PAIN AND CANCER

Using virtual reality to lesson the pain during child birth and anxiety during chemotherapy

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VIRTUAL REALITY AND LABOR PAIN

"FEDERICO II" SCHOOL OF MEDICINE AND SURGERY

WHAT IS THE FUNCTION OF PAIN?

Pain demands attention

(Eccleston and Crombez 1999)


Attention is a finite and shared resource.

Pain and Anxiety

Anxiety worsens pain

- anxiety levels have been shown to predict pain severity and pain behavior in acute and chronic pain patients (Kain et al. 2000) ;
- anxiolytic drugs have been reported to be successful in ameliorating pain associated with medical procedures (Suls and Wan, 1989) .

Common used pharmacologic methods of pain reduction may produce anxiety as well as other side effects

Standard TX for labor pain

Locoregional anesthesia

Type: epidural

Bupivacaine or fentanyl

IM or IV anesthesia

Pethidine, diamorphine, other opioids

Inhalatory analgesia

Nitrous oxide

Why VR may be a better alternative than pharmacologic means

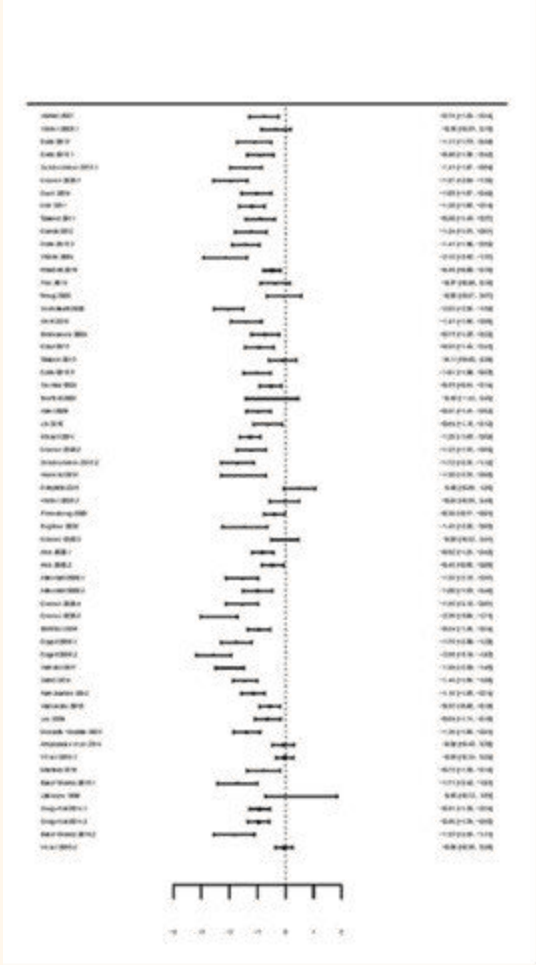
A meta study by our group

Goal

To evaluate the efficacy of non-pharmacological and non-invasive analgesic delivery techniques as a reduction of subjective pain.

Why go alternative?

- Limits of pharmacological analgesia
- the satisfaction outcome
- Anxiety and labor fear



In our study we compared VR to other common alternative methods

We looked in depth at 45 studies including studies using:

7 Massage therapy

4 Birth ball

6 distraction / mind-body interventions

7 Heat therapy

7 music therapy

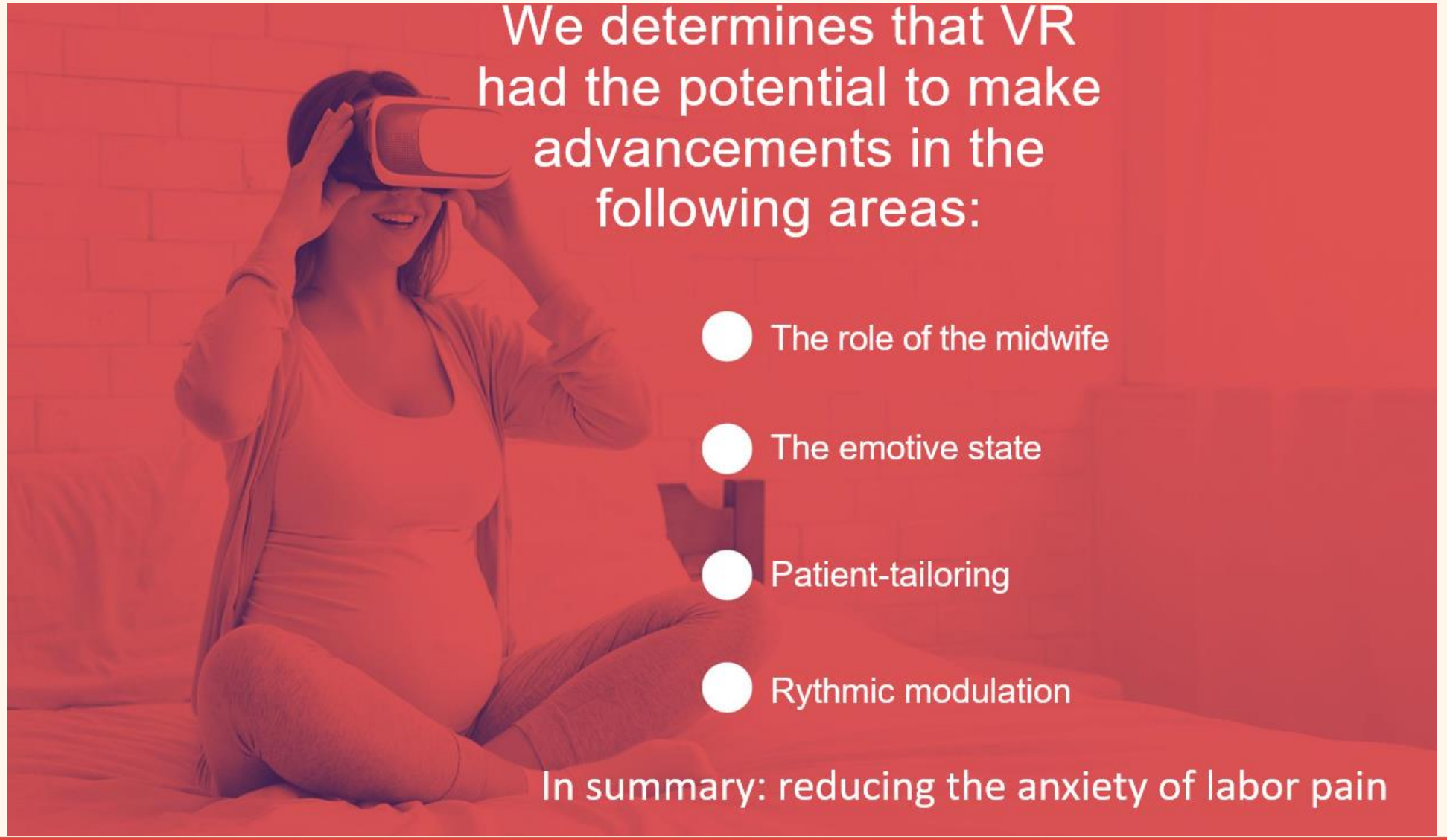
2 dance therapy

12 acupressure

5 TENS

Melillo A, Maiorano P, Rachedi S, Caggianese G, Gragnano E, Gallo L, De Pietro G, Guida M, Giordano A, Chirico A. Labor Analgesia: A Systematic Review and Meta-Analysis of Non-Pharmacological Complementary and Alternative Approaches to Pain during First Stage of Labor. Crit Rev Eukaryot Gene Expr. 2022;32(2):61-89. doi:

10.1615/CritRevEukaryotGeneExpr.2021039986. PMID: 35381132.



We determines that VR had the potential to make advancements in the following areas:

- The role of the midwife
- The emotive state
- Patient-tailoring
- Rythmic modulation

In summary: reducing the anxiety of labor pain

Use of VR for cancer chemotherapy patients

Virtual Reality can lesson the anxiety and alleviate some side effects of cancer chemotherapy in breast cancer patients

Journal of Cellular Physiology WILEY

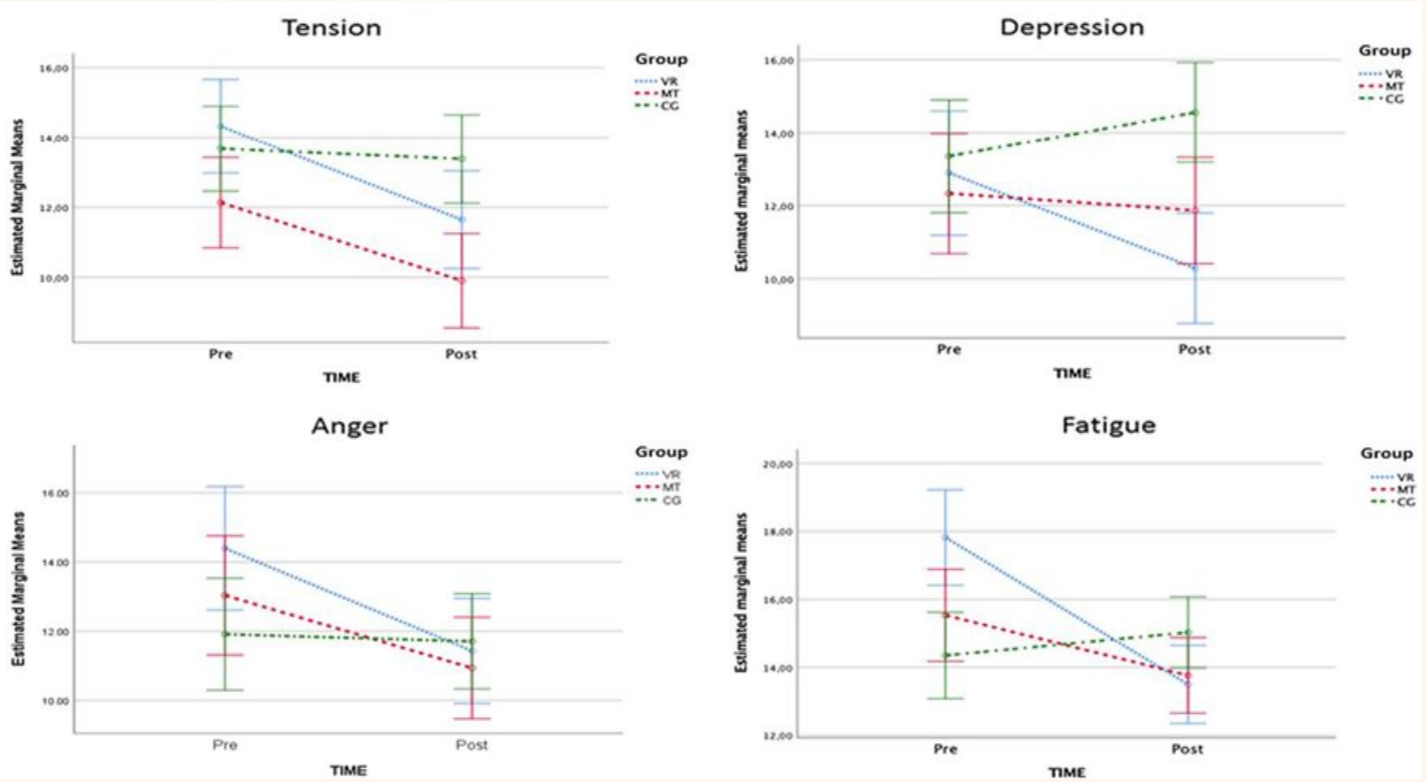
Virtual reality and music therapy acta as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy

- Psychological distress is a common consequence of breast cancer diagnosis and treatment ;
- This distress can further impact on severity of side effects of therapy;
- Intervention that increase treatment tolerance are crucial to improve both patient quality of life and adherence to therapy;
- Using immersive and interactive virtual reality (VR), combined with music therapy as a distraction tool, we have shown this to be useful to improve mood states in breast cancer patients undergoing chemotherapy.

Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, Iodice G, Gallo L, De Pietro G, Lucidi F, Botti G, De Laurentiis M, Giordano A. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. J Cell Physiol. 2020 Jun;235(6):5353-5362.

Virtual Reality (VR) alleviates many adverse events related to cancer chemotherapy

Results showed that incorporation of virtual reality algorithms significantly **REDUCES** the feelings of tension, depression, anger, and fatigue experienced by breast cancer patients who were undergoing chemotherapy



Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, Iodice G, Gallo L, De Pietro G, Lucidi F, Botti G, De Laurentiis M, Giordano A. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. J Cell Physiol. 2020 Jun;235(6):5353-5362.

Percentage frequency of the occurrence of each symptom by the items of the Virtual Reality Symptom Questionnaire (VRSQ) shows none to slight incidence of adverse events from VR therapy.

This shows that VR can be used safely by a wide variety of patients and is successful at lessening their chemotherapy induced side effects

Symptom	None 0	Slight		Moderate		Severe	
		1	2	3	4	5	6
General discomfort	82.1	3.6	7.1	0	7.1	7.1	0
Fatigue	78.6	7.1	0	0	7.1	7.1	0
Boredom	57.1	17.9	7.1	0	10.7	7.1	0
Drowsiness	50.0	17.9	7.1	3.6	10.7	7.1	3.6
Headache	67.9	10.7	10.7	0	3.6	3.6	3.6
Dizziness	89.3	3.6	7.1	0	0	0	0
DIfficulty concentrating	64.3	14.3	21.4	0	0	0	0
Nausea	85.7	3.6	7.1	0	3.6	0	0
Tired eyes	67.9	10.7	7.1	3.6	10.7	0	0
Aching eyes	82.1	7.1	10.7	0	0	0	0
Eyestrain	78.6	17.9	0	3.6	0	0	0
Blurred	82.1	10.7	7.1	0	0	0	0
Difficulties focusing	78.6	3.1	2.1	0	0	0	3.6

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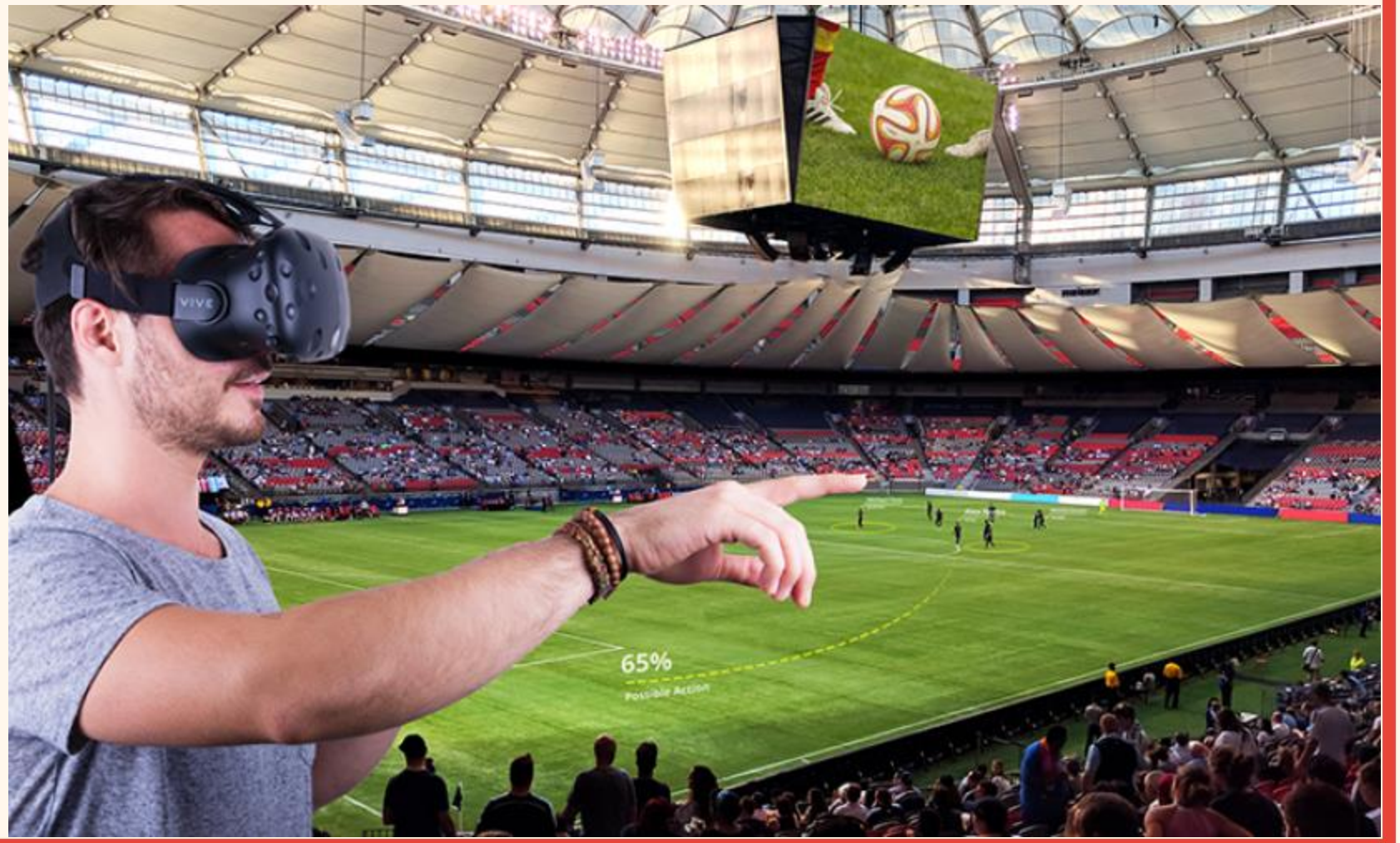
Sports Injury, Rehabilitation and VR

Combining VR with molecular tools to enhance sports related recovery

“Necessity is the Mother of Invention”

Plato



We performed genomic analysis on Napoli soccer team players to determine genetic polymorphisms which might indicate which rehabilitative treatment they should receive

These results are indicated in the following slides

Journal of Cellular Physiology WILEY

Genomic analysis reveals association of specific SNPs with athletic performance and susceptibility to injuries in professional soccer players

Raffaele La Montagna et al

The development of specific and individualized training programs is a possible way to improve athletic performance and minimize injuries in professional athletes. The information regarding the sport's physical demands and the athletes' physical profile have been, so far, considered as exhaustive for the design of effective training programs. However, it is currently emerging that the genetic profile has to be also taken into consideration. By merging medical and genetic data, it is thus possible to identify the athlete's specific attitude to respond to training, diet, and physical stress. In this context, we performed a study in which 30 professional soccer players, subjected to standard sport medical evaluation and practices, were also screened for genetic polymorphism in five key genes (*ACTN3, COL5A1, MCT1, VEGF*, and *HFE*). The genetic fingerprinting of single athletes led to the identification of two performance-enhancing polymorphisms (ACTN3 18705C>T, VEGF-634C>G) significantly enriched. Moreover, we derived a genetic model based on the gene set analyzed, which was tentatively used to reduce athletes' predisposition to injuries, by dictating a personalized nutrition and training program. **The potential usefulness of this approach is concordant with data showing that this team has been classified as the healthiest and least injured team in Europe while covering the highest distance/match with the highest number of high-intensity actions/match**.

Journal of Cellular Physiology WILEY

Genomic analysis reveals association of specific SNPs with athletic performance and susceptibility to injuries in professional soccer players

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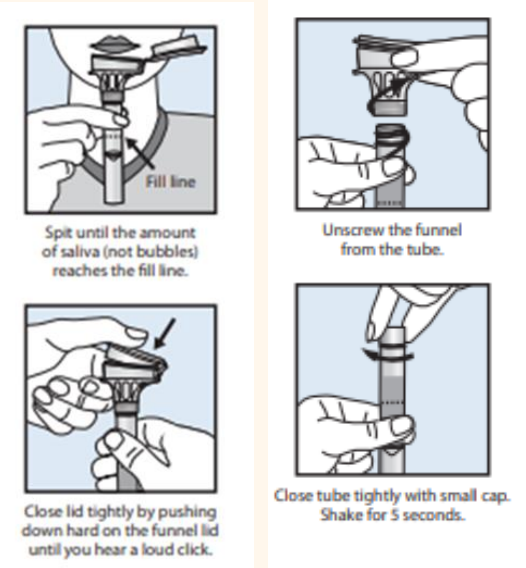
- We performed a study in which **30 professional soccer players**, subjected to standard sport medical evaluation and practices, were also screened for genetic polymorphism in **five key genes (*ACTN3, COL5A1, MCT1, VEGF*, and *HFE*);**

La Montagna R, Canonico R, Alfano L, Bucci E, Boffo S, Staiano L, Fulco B, D'Andrea E, De Nicola A, Maiorano P, D'Angelo C, Chirico A, De Nicola A, Giordano A. Genomic analysis reveals association of specific SNPs with athletic performance and susceptibility to injuries in professional soccer players. J Cell Physiol. 2020 Mar;235(3):2139-2148.

METHODS

1. SAMPLE COLLECTION AND GENOMIC DNA EXTRACTION

For each soccer players was collected 2 mL of saliva using a painless and non invasive device.
The DNA extraction was performed using a specific kit, following manufactory instructions.

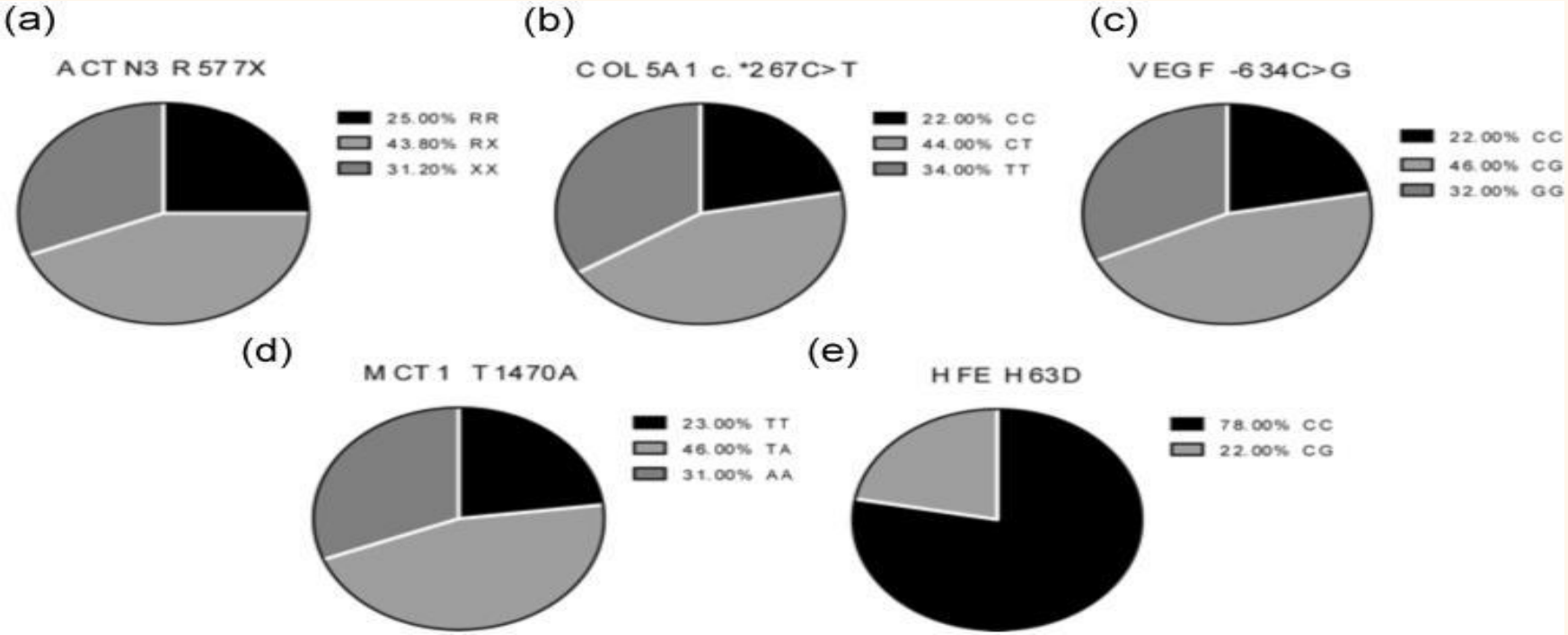


2. GENOTYPING

For the evaluation of SNPs in the HFE, COL5A1, ACTN3, and VEGF, we performed an allelic discrimination by real-time PCR.
For the evaluation of SNP in the MCT1 gene, we amplified the genomic DNA by using PCR. The PCR product was analyzed on the 1% agarose gel, extracted and the samples were then sequenced.

WILEY–Journal of Cellular Physiology

Results of genetic screening showed performance-enhancing polymorphisms in Naples soccer players



Distribution and frequency of performance-enhancing polymorphisms in S.S.C. Naples soccer players. (a–e) Genes, alleles, and genotype frequency in the 30 S.S.C. Naples soccer players. In black, the homozygous wild type genotype; in light gray, the heterozygous and in the dark gray, the homozygous polymorphic genotype.

WILEY- Journal of Cellular Physiology

- The genetic fingerprinting of single athletes led to the identification of two performance-enhancing polymorphisms (ACTN3 18705C>T, VEGF-634C>G) significantly enriched We performed a study in which 30 professional soccer players, subjected to standard sport medical evaluation and practices, were also screened for genetic polymorphism in five key genes (*ACTN3, COL5A1, MCT1, VEGF*, and *HFE*);

- We derived a genetic model based on the gene set analyzed, which was tentatively used to reduce athletes' predisposition to injuries, by dictating a personalized nutrition and training program;

- **The potential usefulness of this approach is concordant with data showing that this team has been classified as the healthiest and least injured team in Europe while covering the highest distance/match with the highest number of high-intensity actions/match**

La Montagna R, Canonico R, Alfano L, Bucci E, Boffo S, Staiano L, Fulco B, D'Andrea E, De Nicola A, Maiorano P, D'Angelo C, Chirico A, De Nicola A, Giordano A. Genomic analysis reveals association of specific SNPs with athletic performance and susceptibility to injuries in professional soccer players. J Cell Physiol. 2020 Mar;235(3):2139-2148.

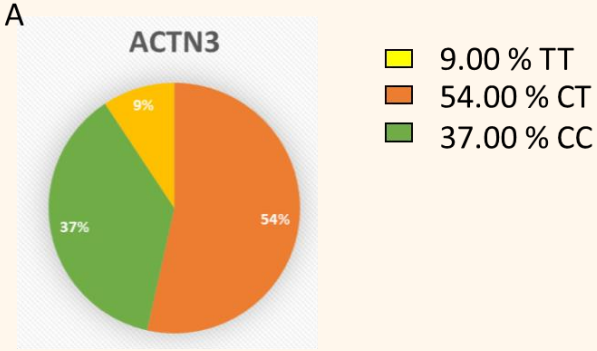
The same genomic analysis was performed on Fiorentina soccer team players to determine genetic polymorphisms that might indicate the rehabilitative treatment they should receive.

We performed a study in which **43 professional soccer players** (22 female and 21 male), were screened for genetic polymorphisms in four key genes (*ACTN3, COL5A1, VEGF*, and *HFE*).

Preliminary results are presented in the following sections

Preliminary results of genetic screening on performance-enhancing polymorphisms in Fiorentina soccer players

A



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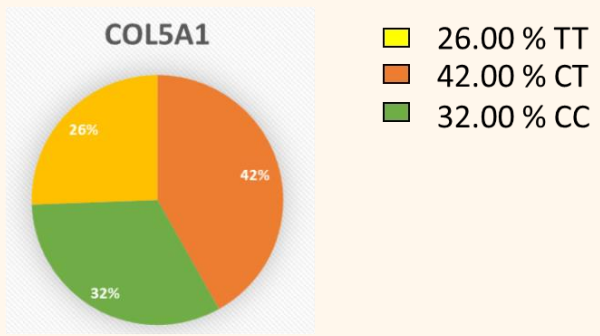

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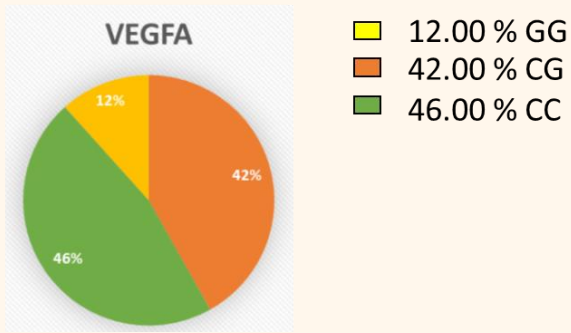

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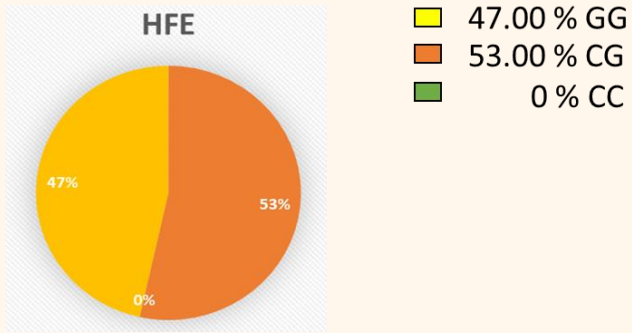

Distribution and frequency of polymorphisms in ACF Fiorentina soccer players (A–D) Genes, alleles, and genotype frequency in the 43 ACF Fiorentina soccer players. In **green**, the homozygous wild type genotype; in **orange,** the heterozygous and in **yellow**, the homozygous polymorphic genotype

Raw data obtained from the preliminary analysis will be analyzed to assess the significance of the results.

The aim of our work is to develop a **gene test** capable of identifying SNPs and quantifying the relative risk of each athlete suffering a certain type of injury by simply taking a saliva sample.

Comparable to the study we have done with Napoli and Fiorentina soccer players we intend to extend these studies to Real Madrid

Thank you to our partners!

Professor Antonio Giordano with President of S.S.C Napoli Aurelio De Laurentiis

Professor Antonio Giordano with President of ACF Fiorentina Rocco Commisso and general manager Giuseppe Barone

Professor Antonio Giordano with the coach Luciano Spalletti

Professor Antonio Giordano with the coach Carlo Ancelotti

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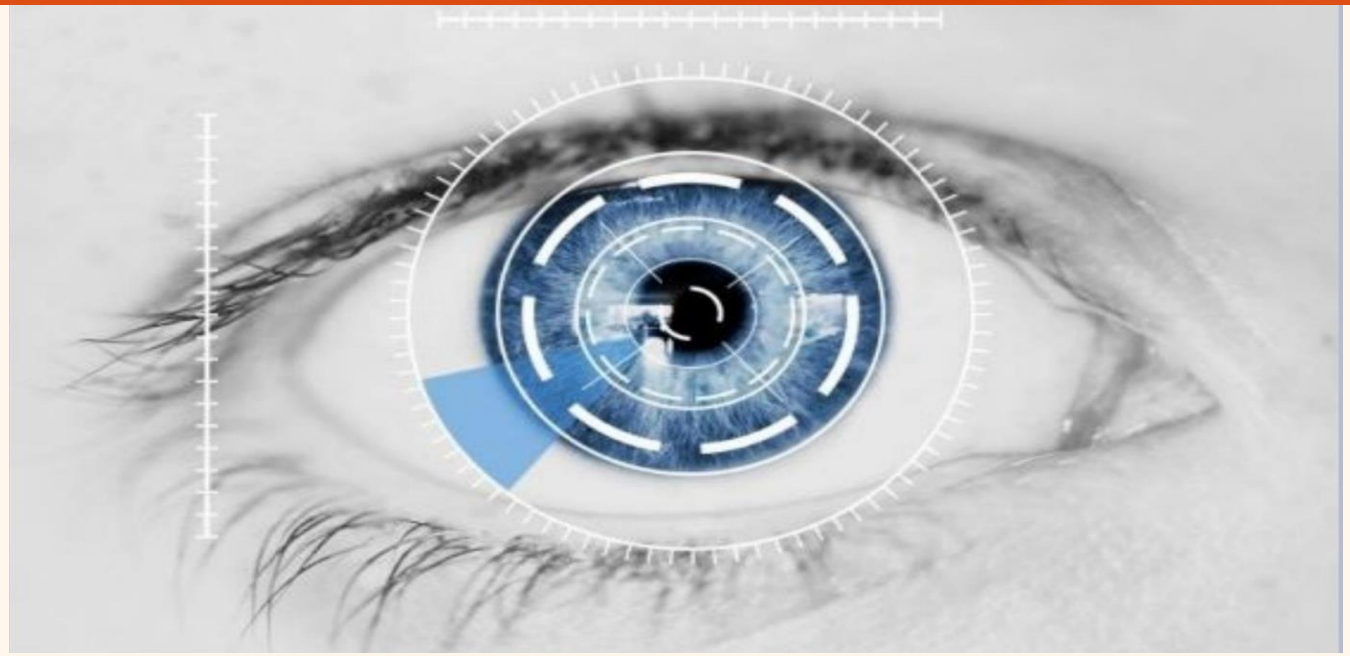
Combining technologies Virtual Reality and eye tracking for sports with aiming task



There are some indicators that could be associate to gaze behavior and sports performance: the quiet eye

The study of ocular behaviors, in particular of the fixation strategies of athletes, allow us to:

- Predict the quality of the performance;
- Know the mental processes that underlie the performance;
- Intervene with specific training to improve virtuous eye strategies;
- Monitor the effectiveness of the specific technical training and mental training program aimed at improving performance.

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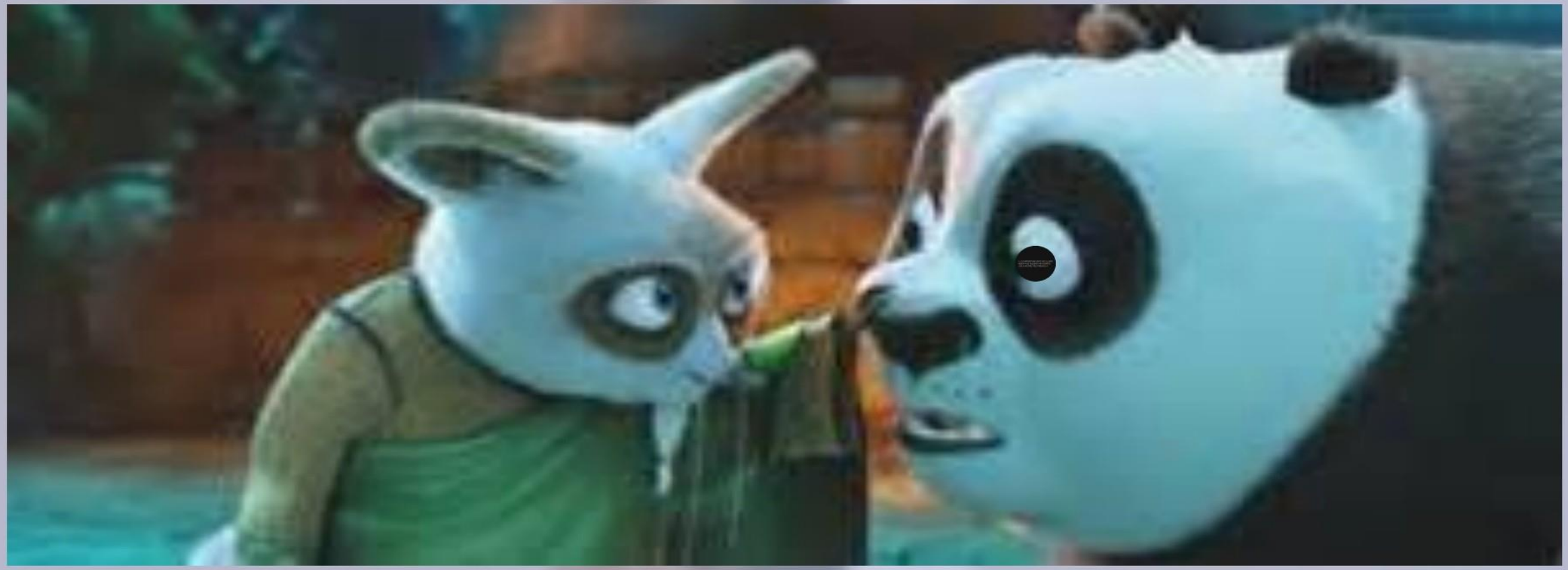
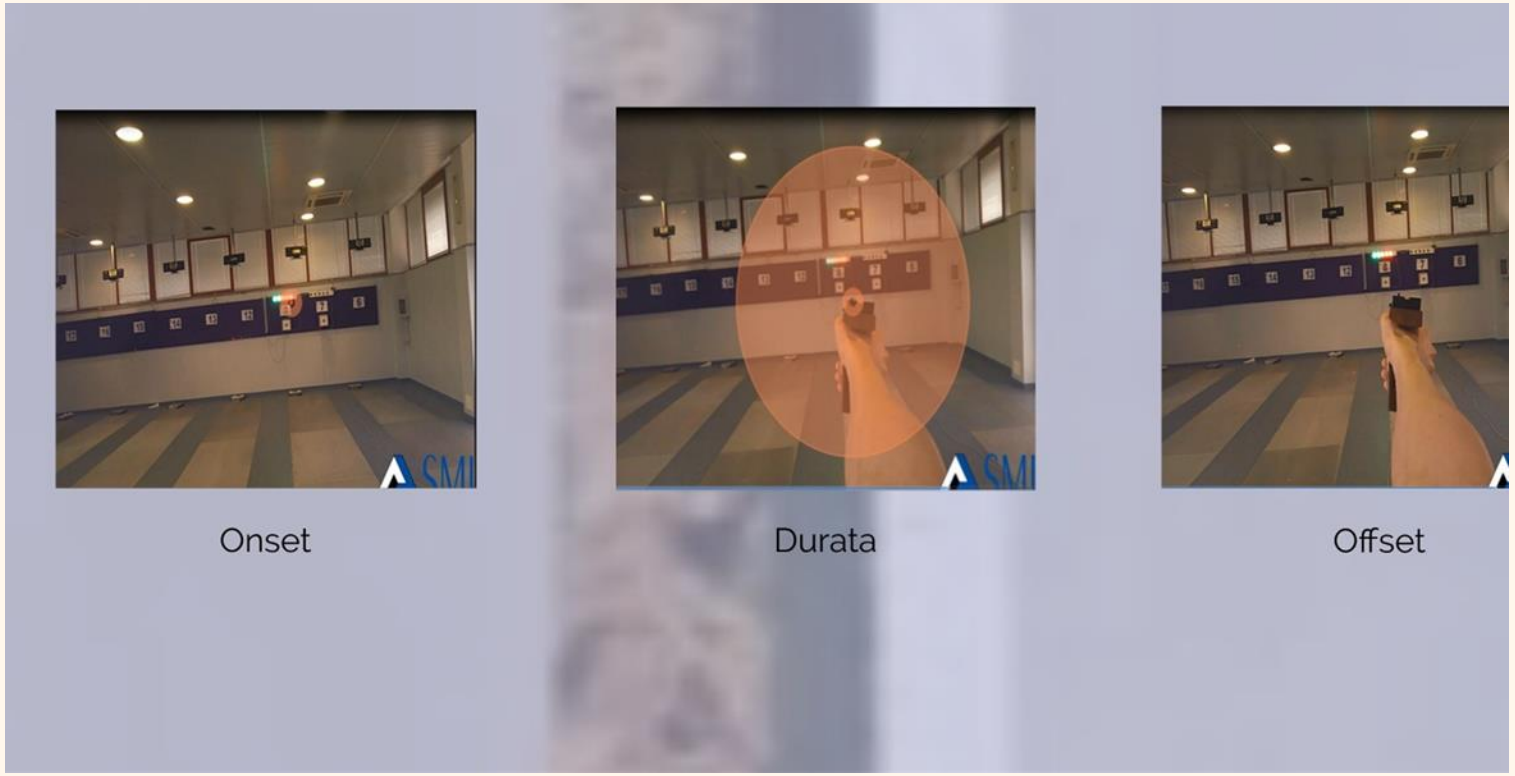
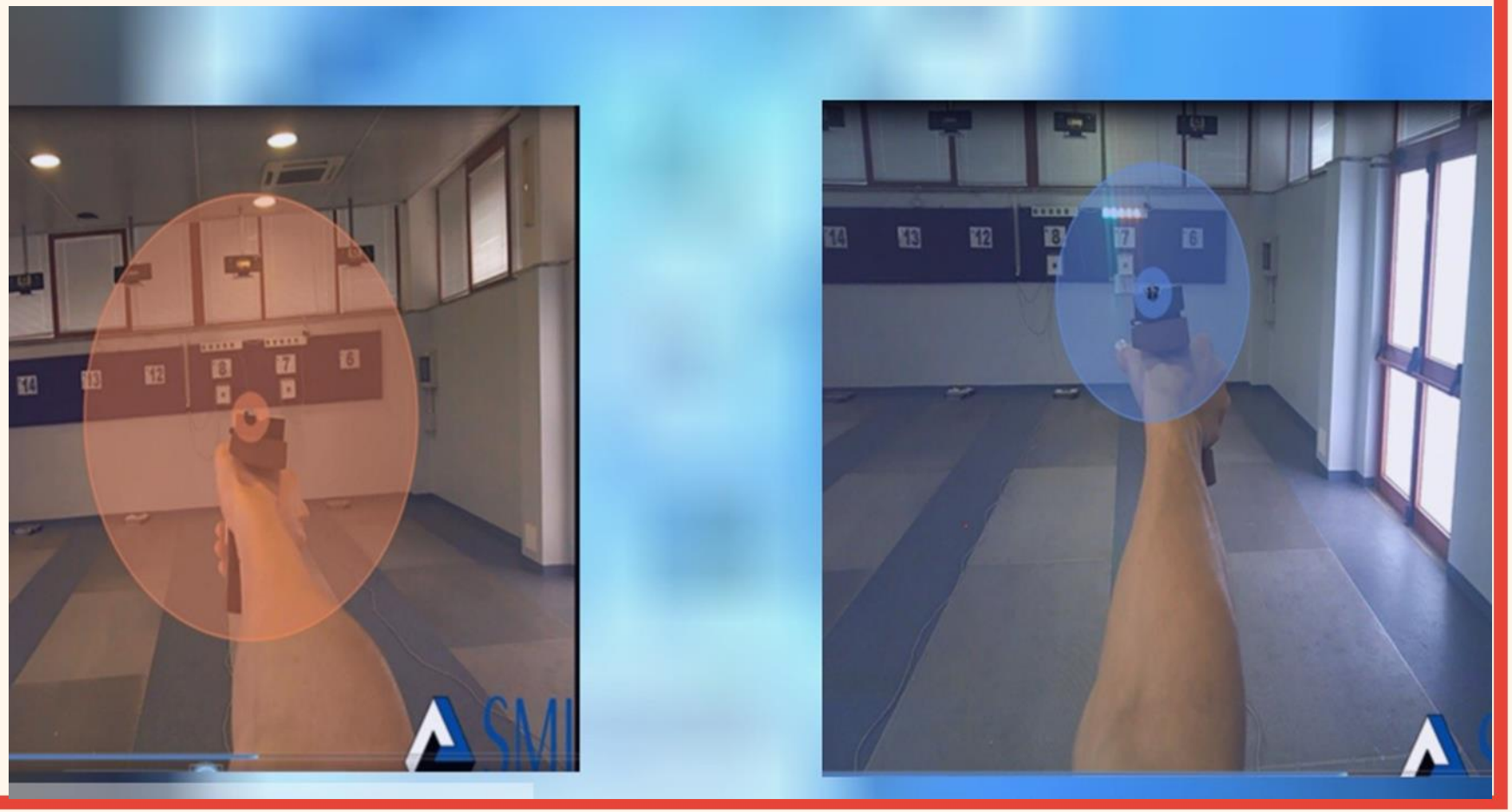


Eye tracker and penthatlon

Different parameters of the Quiet eye are related to performances



Same athlete – no time pressure (right side) vs time pressure (left side)



ORIGINAL RESEARCH ARTICLE

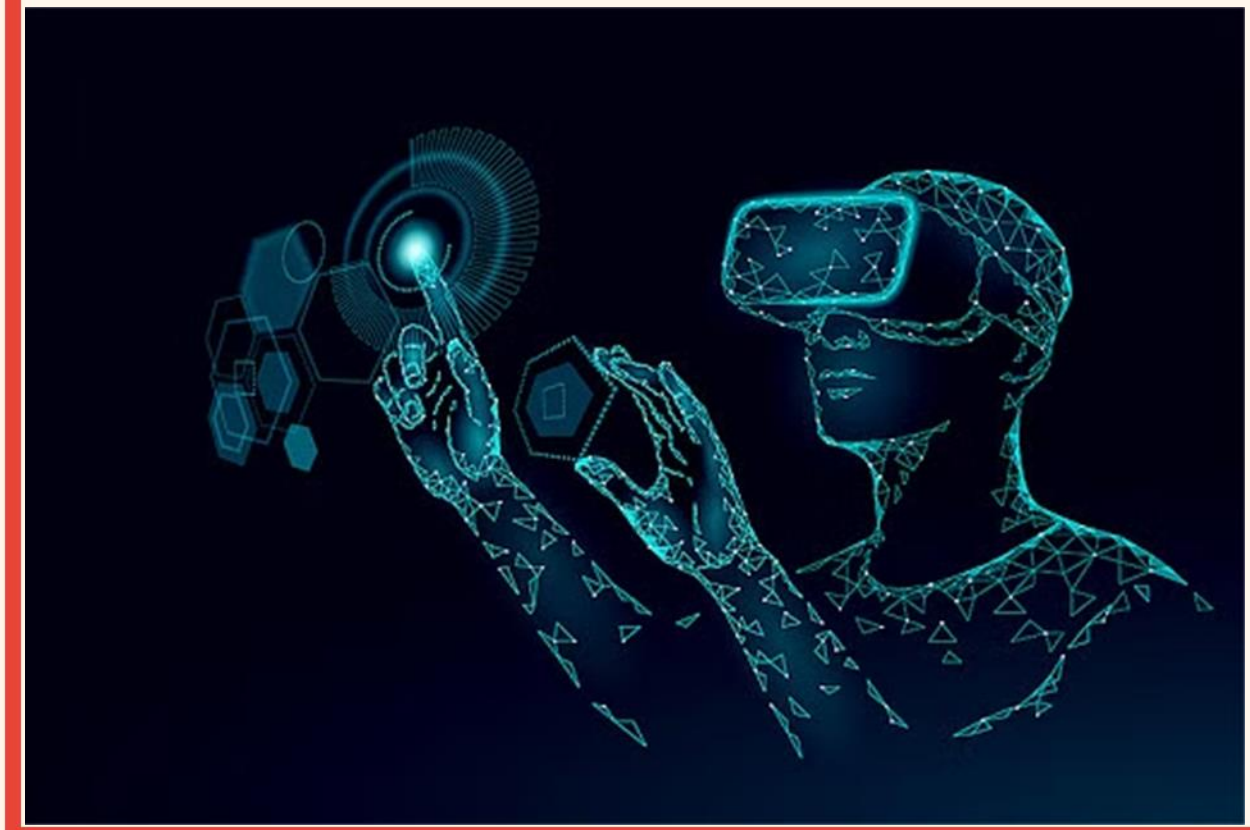
WILEY Cellular Physiology

A study of quiet eye's phenomenon in the shooting section of "laser run" of modern pentathlon

Andrea Chirico[1,2] | Dario Fegatelli[1] | Federica Galli[1] | Luca Mallia[3] | Fabio Alivernini[4] | Susanna Cordone[1] | Francesco Giancamilli[1] | Stefano Pecci[5] | Gian Marco Tosi[6] | Antonio Giordano[2,7] | Fabio Lucidi[1] | Mina Massaro[8]

The results revealed that both groups of athletes had a longer QED, RQED, and an earlier onset during their best shots than during the worse ones. Furthermore, differences between the groups showed that elite athletes had an earlier onset and a shorter QED than the novice group of athletes. These results provide insightful information about different cognitive and perceptual processes involved in Modern Pentathlon's athletes' performances at both the elite and non- elite level.

Future:
Merging Quiet eye results for training in VR



IV CONGRESSO NAZIONALE

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eXtending the Reality in Cardiology

Future:
From Virtual to *eXtended* Reality

Visual assistance system for Transcatheter Aortic Valve Implantation (TAVI) interventions

Objectives:

Support the cardiologist in the accurate positioning of the prosthetic valve

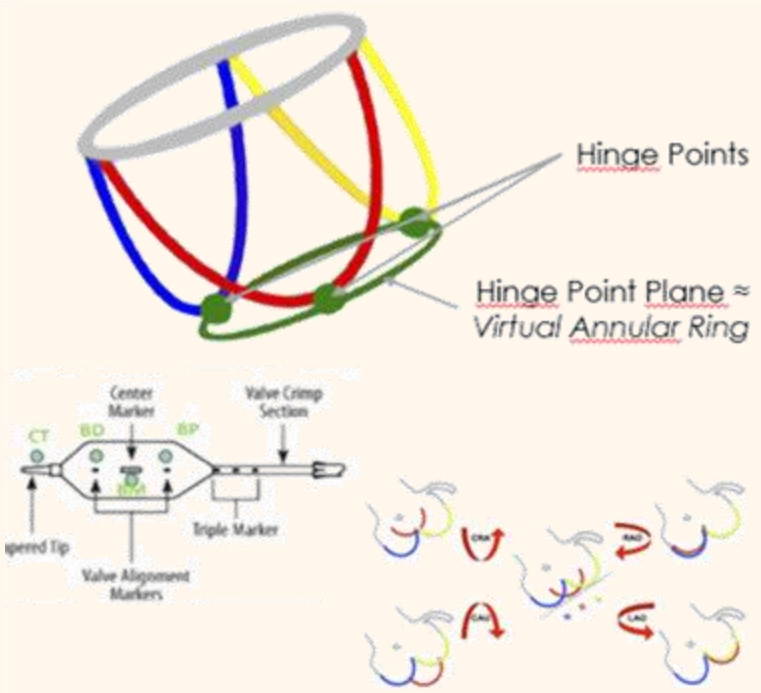
Reduce the volume of contrast media

Reduce the duration of the intervention

Visual assistance system for Transcatheter Aortic Valve Implantation (TAVI) interventions

Research:

- Deep neural network for the identification of both the hinge points (aortic valve anatomical landmarks) and the keypoints of the delivery system
- Automatic configuration of the image acquisition equipment
- Tracking of position and orientation of the hinge point plane in absence of contrast media
- Automatic 3D positioning of the virtual prosthetic valve
- In situ augmented visualization and real-time matching of position and orientation of virtual and real valves



Future Considerations for Virtual Reality, Genetic Analysis and Rehabilitation

Comparable to the study we have done with Napoli soccer players we intend to extend these studies to

Fiorentina players

Players from Real Madrid

The combination of virtual reality with genomic analysis can be a powerful tool to determine patients that will respond best to a personalized rehabilitation treatment schedule

We also intend to extend our studies with cancer patients to further determine the ability of VR to lesson side effects of cancer treatment and also to lesson effects of PSTD

IV CONGRESSO NAZIONALE

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Dott.ssa Iris Maria Forte
Dott.ssa Carmelina A. Iannuzzi
Dott. Luigi Alfano