# Biomaterials Enhanced Simulation Test: as alternative towards true 1R implementation

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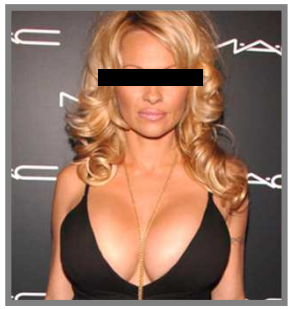
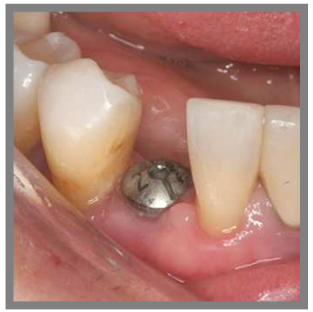
ACTION MP1301

# The Grand Challenge

**Development of better and safer implants, eliminating the need for revisions due to loosening, degradation and infections**

Aesthetic ⟷ Functional





| | | | |
|---|---|---|---|
| Yearly: | <…….> | >1,300,000 | ~500-2000 / 1M capita |
| **Complications!** | **20-50%** | **2-15 %** | **2-14 %** |

**Surgeons' verdict:**

"There is **little or no scientific evidence** that newer prostheses are better. The success of implants is guided by **quality of biomaterials.**"

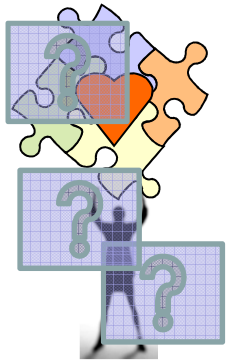
# Market key drivers

- Increased **lengths of hospital stay** and **risk of complications**, supply, etc.
- New **technological advancements** coming (flowable allografts, bone glues)
- **Demographic** factors (increased arthritis, osteoporosis, elderly population, obesity, etc.).
- Patients demanding **alternatives** to TJA to extend their physically active lives → postponing major surgeries
- Significant need remain for **soft tissue reinforcement grafts** in sports medicine applications (traumas → faster recovery)

- To **develop alternates** to the "gold standards" under healthcare financial constrains
- Products **assessment and validation** still in its infancy
- More pressure to develop and market **better biomaterials** and ATMP solutions
- Only possible with **new validated solutions** (xeno-implantation, allografts, syntgrafts) – require efforts in their analysis
- **Higher requirements** for these solutions vs. general cases. Need for **difficult and 'uncommon' joints** repair (fingers, rotator cuff, Achilles tendon, knee ligament, cartilage)

**World-wide growing** biomaterials **market**:
**$62,060 millions** (2015) → **$130,570 millions** in 2020 (CAGR 16%)

# What are the problems



- Biomaterials need a very high confidence, but no one waits for 10 years follow-up results → **lost time and momentum, legal actions risks, obsolete medical technology**
- Biomaterials evaluation limited to too oversimplified tests and too expensive *in vivo* tests ("successful *in vivo*" → 80-95% fail in clinical trials*) → **billions €€€ spent; animals killed for none**
- New regulatory issues require a scientifically based evidence → **tougher risks and quality management**, new special NB for Class IIa/III, **no "grandfathering"**!
- Changes in the conformity assessment ongoing → the **transition clock is down counting** for implants and MD producers

True stories:

DePuy → losses ~$2.5B in 2013 to cover hip implants failure caused injuries.

Zimmer → NextGen (2010) and Persona (2015) knee implants withdrawn from the market

** FICAM / EVCAM data, 2014*

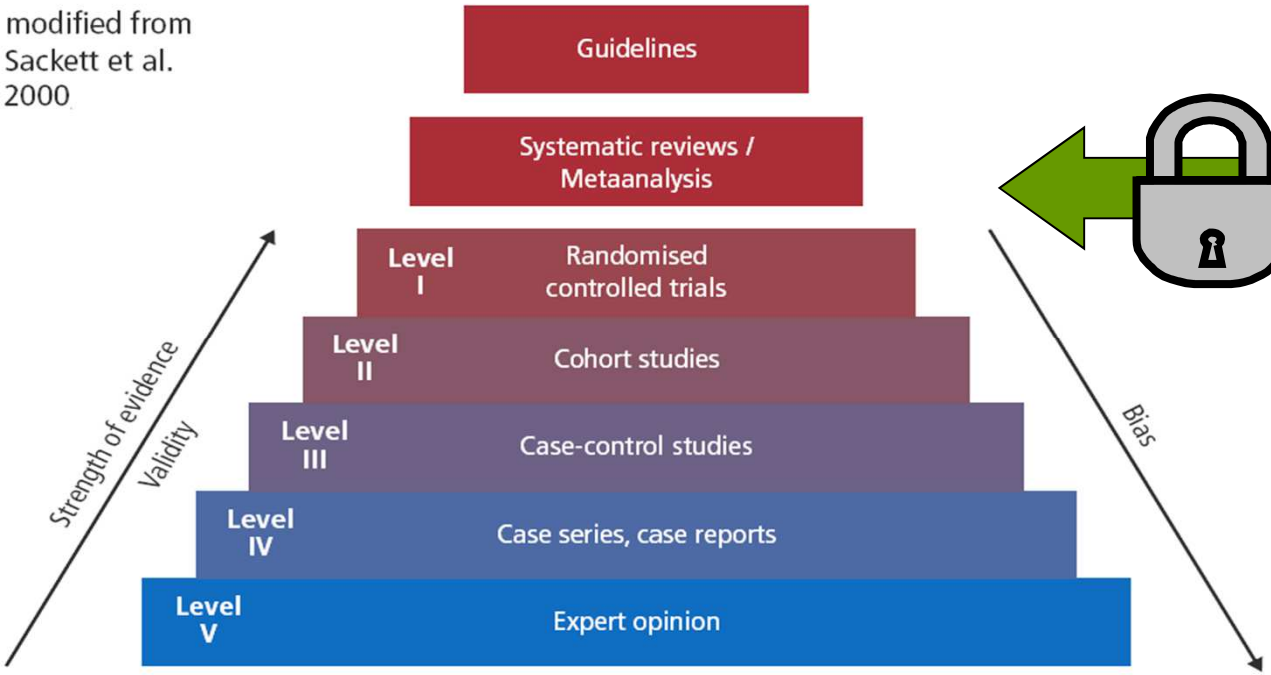
# Evidence-based Medicine?

- The **need for good-quality evidence** is vital for any medical technology or therapy development.
- There is **a continuous lack of a level of evidence** (LoE) **established in many studies**: publications are often heterogeneous or incomplete, making it difficult for clinicians to evaluate the actual LoE of results and recommendations.
  - For example, orthopaedic registers differ in methods of data analysis, have unavoidable errors and variations in reporting → limits the interpretation, makes comparisons difficult.
  - In one national hip register, error of 50-55% was estimated (wrong bed, age, gender, missing and incomplete information, etc.)
- **How to improve the evidence level?**

# Where is the evidence?

## Clinical evidence

modified from Sackett et al. 2000




## But where is *in vitro* LoE?



ISO standards..
OECD regulations..
EU directives..
FDA guidelines..
In-house practices..
"my own experience"..
"someone said"…

**Where's the key?**

Proper **quantification, scientific validation and documentation** of *in vitro* evidence are prerequisites for successful breakthroughs in 3R and true 1R implementation for medical devices, ATMP and pharma products

# LoE problem example

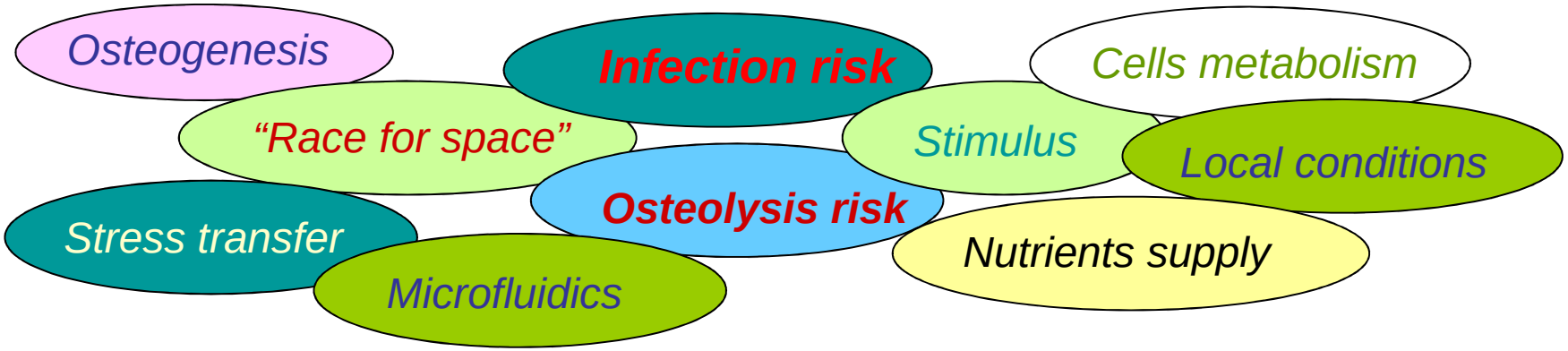
Orthopaedic case

Target: THA

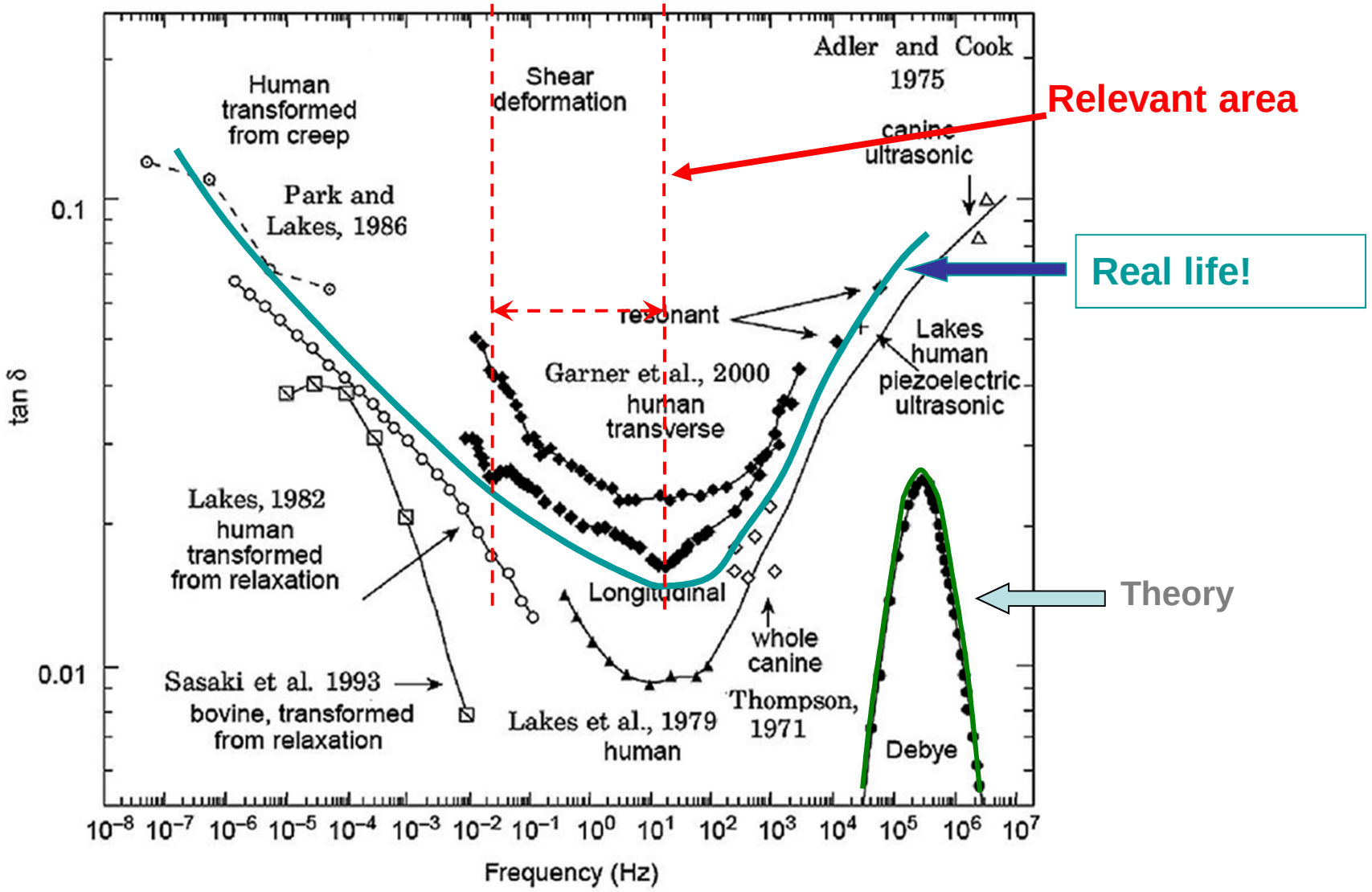
Material: porous/coated Ti alloy

*Usual requirements evaluated in separate tests:*

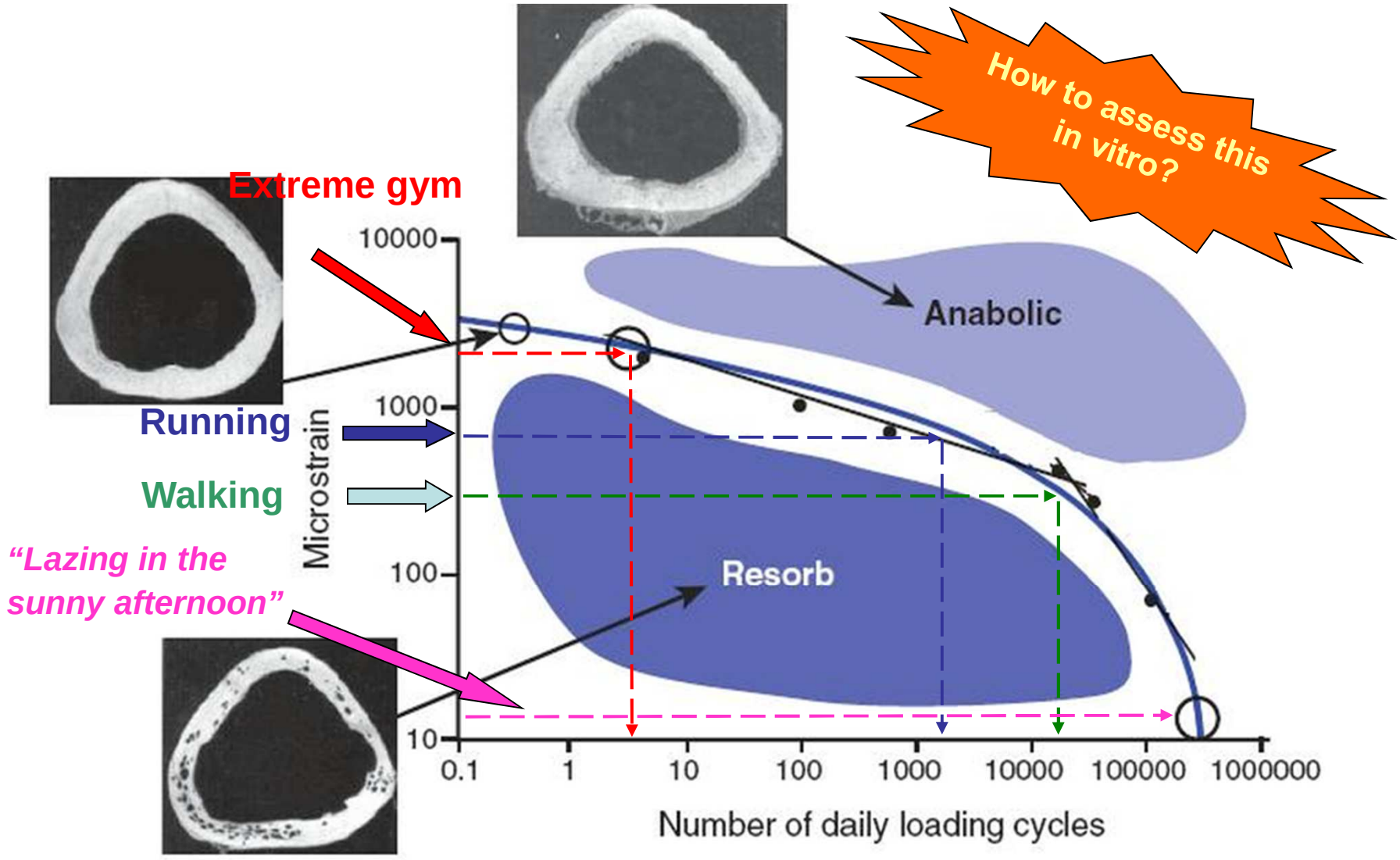

**But what do these tests answer about:**



# Does theory tell true: viscoelasticity of bone



# Viscoelastic fate of bone



# Biomaterials testing objectives

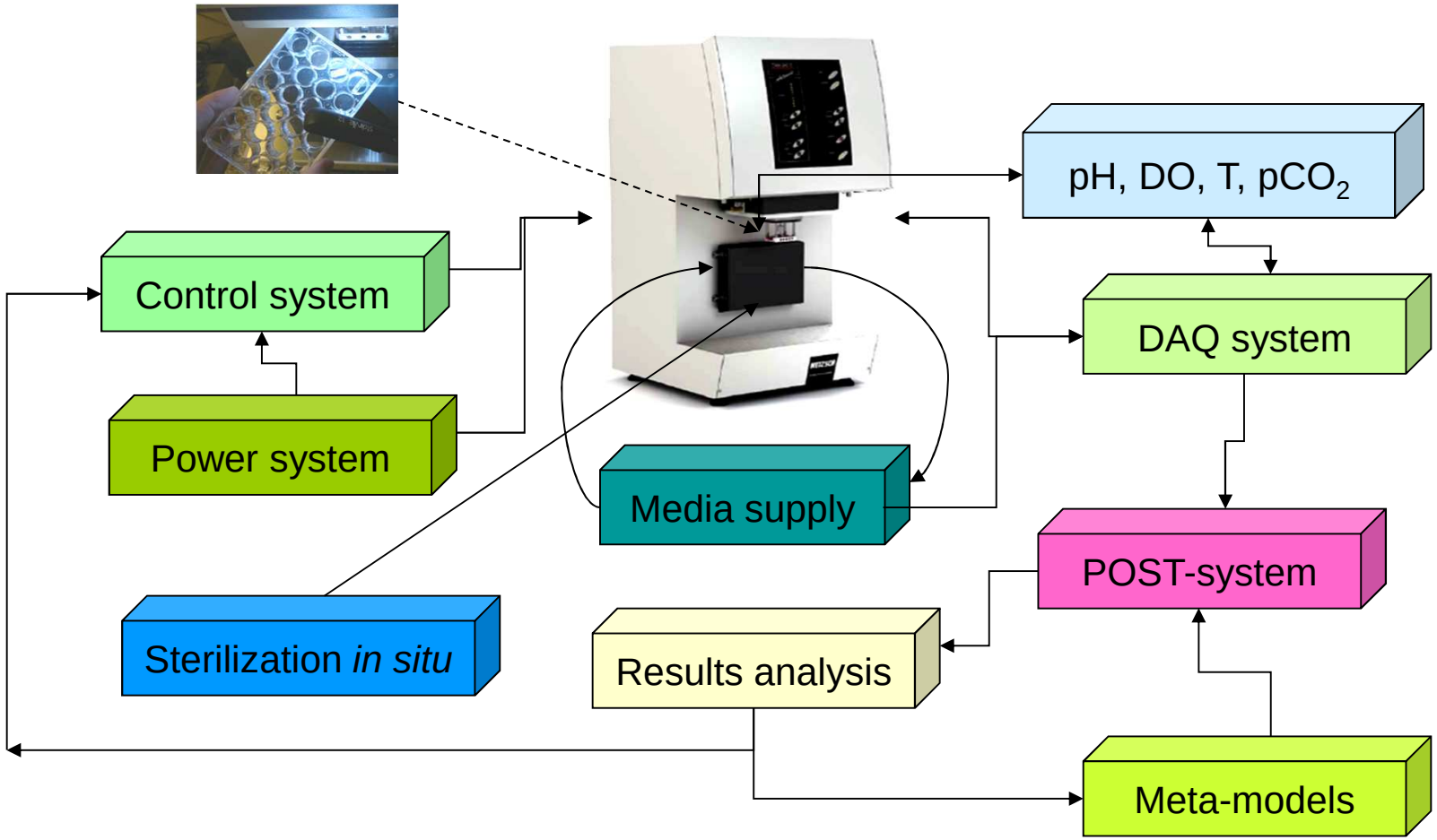
**Biomaterials must be evaluated in the closest host-like *in vitro* environments, with relevant control of chemical, biological, cytological etc. reactions.**

**based on:**

- **Conditions closest to real life applications**, scientifically **designed and optimized**, aiming on predictive outputs (2012/0266/COD)
- Combination of critical **key parameters in minimal tests**, reducing number of specimens, enabling **high-throughput** screening
- **Minimization** animal *in vivo* (2010/63/EC) and clinical tests (2001/20/EC, 2005/28/EC), including “live biomaterials” (ATMP as of 2001/83/EC, 2007/47/EC)
- **Shortening time to market** – eliminating unfeasible solutions at early stages, simulating “worst cases” (2003/94/EC) – a part of quality management and risk minimization actions (2012/0266/COD)

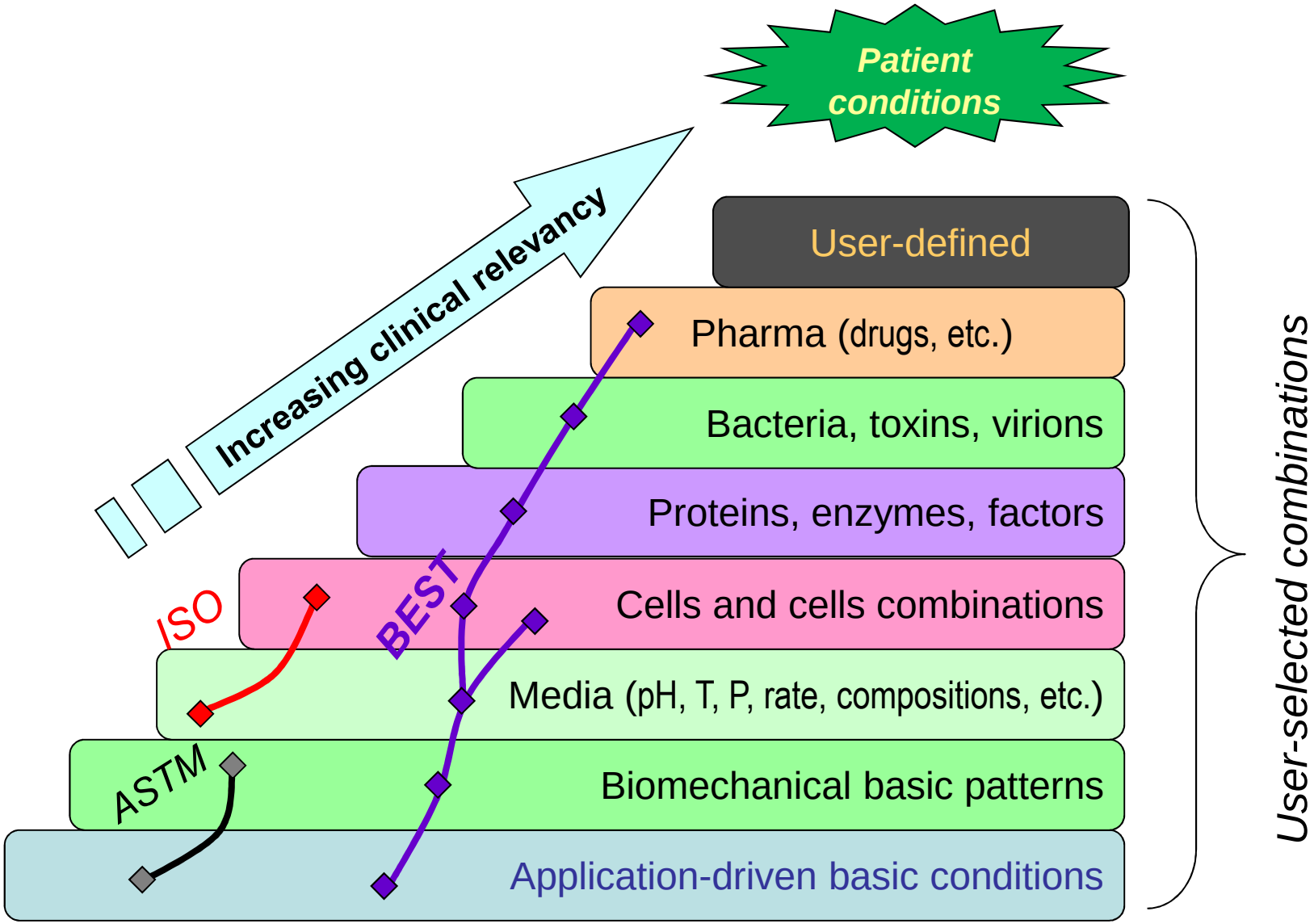
# How this can be done

Introducing **BEST:** the **B**iomaterials **E**nhanced **S**imulation **T**est




*US and EP patents applied*

# BEST protocols for biomaterials

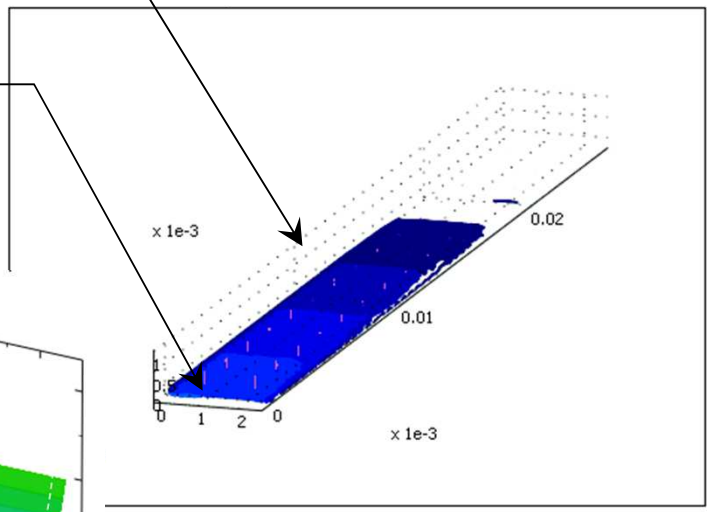


# Evaluation for orthopaedic cases

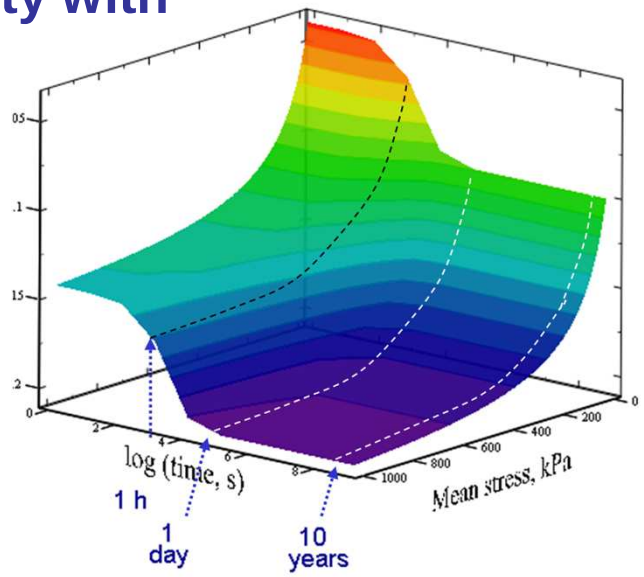
## Different simulation cases to estimate tissue formation probability

***Bone probability: 45%***

***Bone probability: 93%***




**Predictive ability with meta-models:**




**Towards 1R: elimination of animal tests**

# Benefits with a smart biomaterials evaluation

- **Consistent results**: no fragmented and separate tests → reduced risk of improper measurements – fitted to regulatory requirements
- **Synergetic effects** of different parameters revealed → otherwise impossible to obtain
- **Correct effect** of specimen size and boundary conditions → clinically relevant answers
- More **realistic** *in vitro* **conditions** than others → solid evidence – better insurance against claims – less probability of adverse effects
- **Shorter time** for getting the results → higher throughput
- Substantial **costs reduction** → faster and combined experiments
- **Better environmental control**, supported by validated models
- Ability to experiment with **user-specific** and **multi-purpose 'ghost' protocols**

# BEST one can get for a biomaterial:

- **Varieties of biomaterials tested on**:
  - set of biomechanical-fluidic properties in pseudo-static and dynamics
  - static and dynamic permeability / permittivity for porous biomaterials
  - control of (bio)degradation dynamics / kinetics for/with predictive models
  - consistent comparison between different biomaterials (LD/LO)
  - patient surgery protocol mimicking; customized protocols
  - optionally co-cultures (with patogens), toxi- and pharma-tests
  - optimization of conditions for fast throughput and lower costs
  - data for risk reduction (3E) and quality assessment
  - data for 3R and true 1R implementation ("*not tested on animals*")
  - independent expertise of competing MD materials cases – evidence for legal cases
  - extra security for [unannounced] SNB audits
- **BEST is working now for biomaterials in:**
  - dental, macrofacial, cranial, gynaecology, ophthalmology, orthopaedic, plastic surgery, veterinary, ATMP (orthobiology)

# What need we BEST for?

**Example from new MD Directive (2012/0266/COD):**

- prove **MD similarity** for Class III (49 §2.a)
- scientifically **justify equivalency** (XIII.4.a)
- demonstrate earlier **residual risks/effects** (26 §1.a/b)
- verify and validate by tests: **is the MD enough "suited"** (II.6.1)
- enforce **3E for risks management**: "Estimate, Evaluate, Eliminate" (I.1,2.b)
- **demonstrate the compatibility** between materials, tissues and body fluids incorporating processing, modelling, biomechanical properties (I.7)
- prove the tests above **before, during and after manufacturing** (VIII.3.2.e)
- prove elimination/reduction **risk of simultaneous bacterial adhesion** (I.8.1)
- prepare enough information for earlier clinical trials (50 §5)

# SUMMARY

- **A lot of issues still to be resolved for better biomaterials!**
- New solutions vs. costs, community demands, quality/risk control
- **Infections are on the critical level now** → "*race for space*" knowledge and non-antibiotic cure options are insufficient
- **Regulatory pressures** demand higher responsibility from MD manufacturers – but who is paying the bill?
- **Market requires** more efficiency – but financial pressures obstruct: these are not options for patients → suffering, costs, legal, insurance…
- Biomaterials *in vitro* evaluation/screening can be improved with combined scientifically based tests and models with multi-purpose protocols → BEST can secure patient safety of a medical device by certifying biomaterial in hostile-like conditions
- **Multidisciplinary joint effort** is needed from all stakeholders!

# THANK YOU!

**Let’s make NEW GENeneration**

**of biomaterials the BEST one!**