ATMPs in clinical practice, a clinical perspective in cartilage healing

TRIP Biovigilantie, 18-11-2022 Leiden

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Inroduction

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Principle investigator NWA-DARTBAC project

Lid Werkgroep biotechnologie NOV

Lid TRIP Advieskamer Biovigilantie

Building bridges

Maastricht UMC+

Imaging

Clinic/
Medicine

Engineering

Biomaterials

Translational biomaterials research

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Clinical problem	1.	Infection prevention & treatment AntiMicrobial Resistance (AMR)
Clinical problem	2.	Large bone defects
Clinical problem	3.	Spinal deformity

dartbac

prosperos

Spineguide
a BMM project

Chemelot InSciTe
Biomedical materials

Artrose

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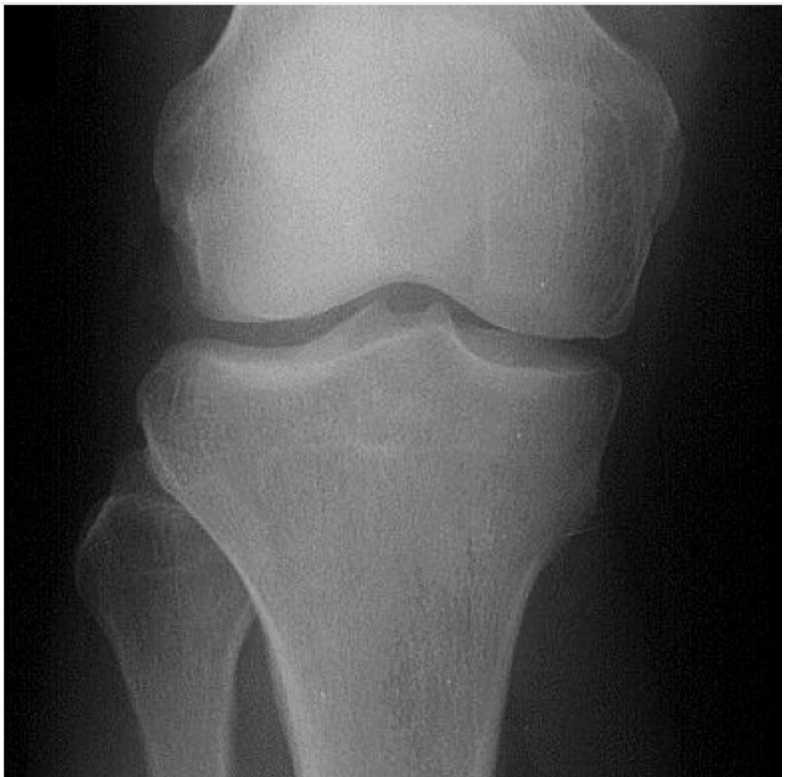
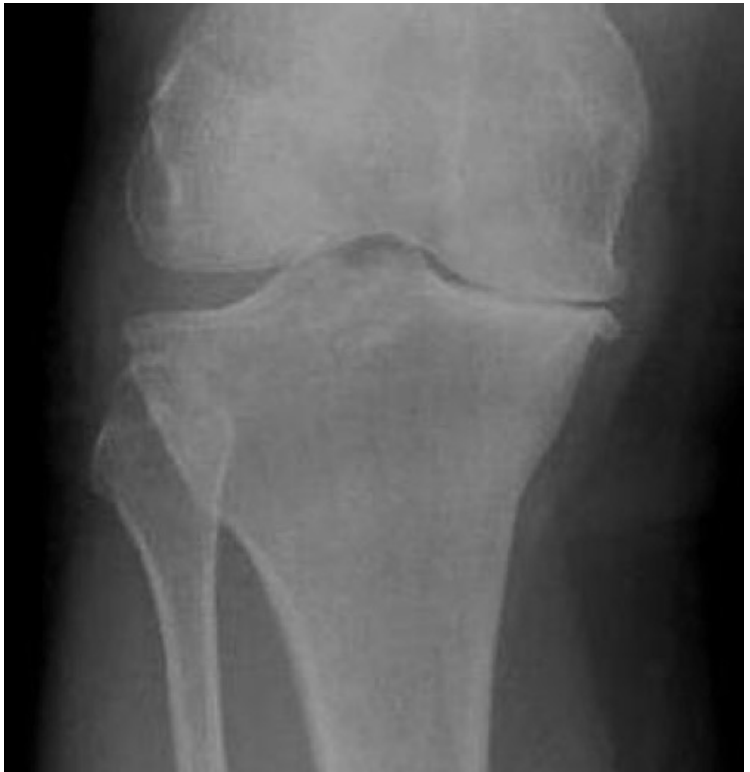
Niet inflammatoire degeneration gewricht

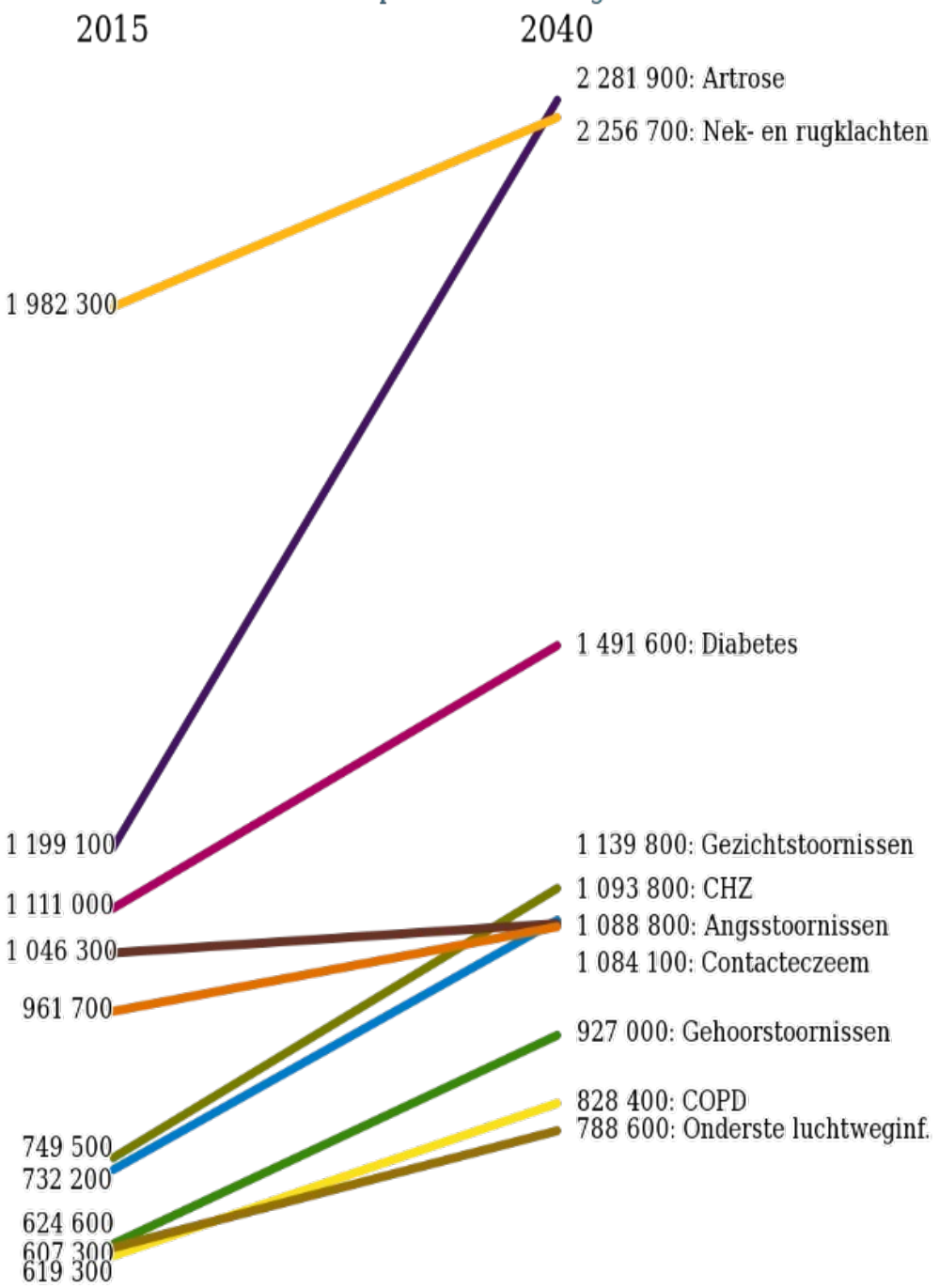
- Sclerose weefsels (verharding weefsels)
- Vernauwing gewrichtsspleetNarrowing joint line
- Subchondrale cystes
- Osteophyt yt (bot uitsteeksels)





Artrose

Burden of disease



Artrose

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Niet inflammatoire degeneratie gewricht

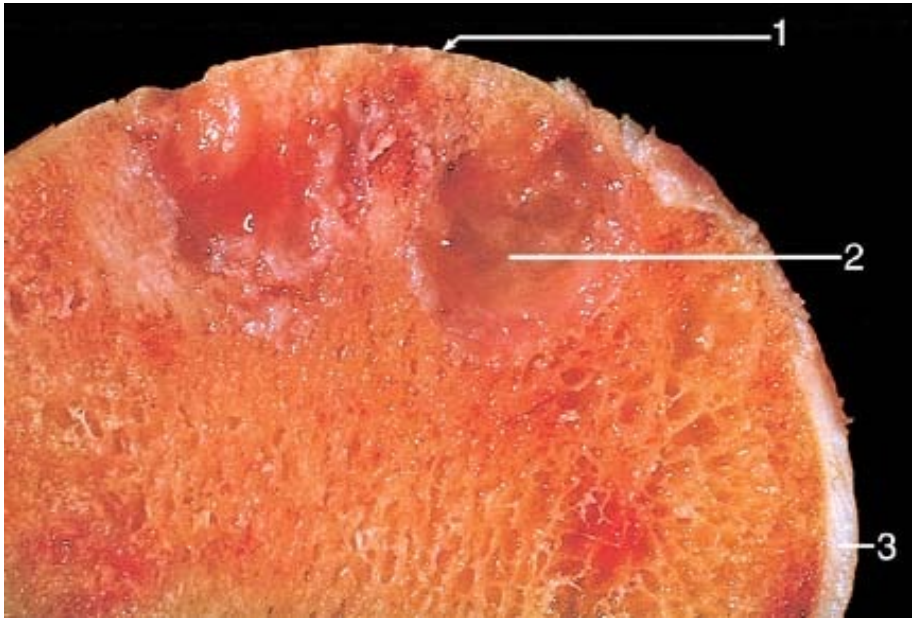
* deformatie bot structuur
* atrofie mucus membraan en kraakbeen

Symptoms

* pijn
* stijfheid
* gelimiteerde functie
* afwijkend looppatroon

Diagnose

* Rx, MRI, CT, bot scan



1= Beschadigd kraakbeen en sclerose
2= Subcondrale cyste
3= Normaal kraakbeen

Chirurgische opties

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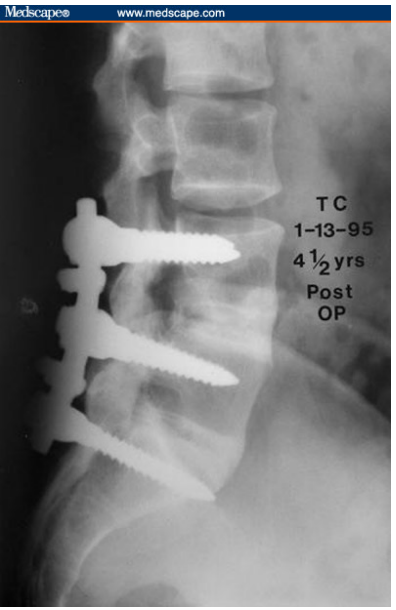
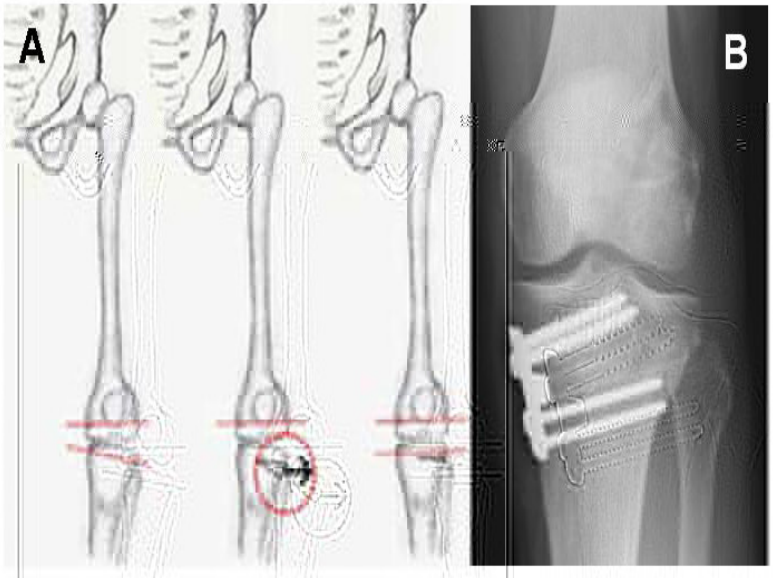


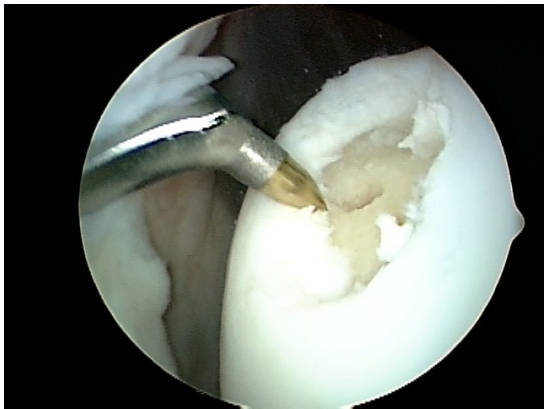
I. Resected (verwijderd) = vastgezet



II. Relieved (ontlast) = bv correctie stand

III. Replaced (vervangen) = prothese

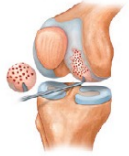
IV. Restored (hersteld) = kraakbeen herstel



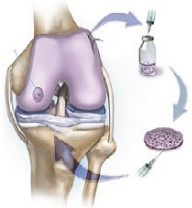
Artrose behandel algorithme

Intra-Articular Surgery

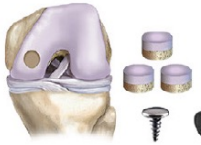
Microfracture & subchondral drilling



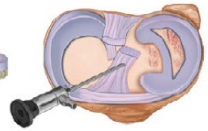
ACI and MACI



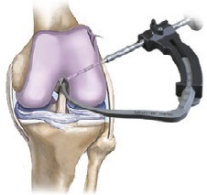
Autografting / Allografting / FKRI



Meniscus repair

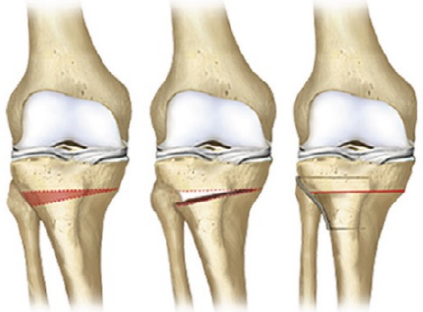


Ligament reconstruction

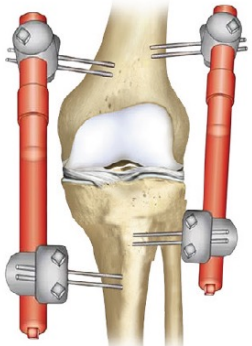


Extra-Articular Surgery

Osteotomy



Distraction

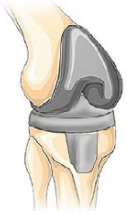


Lifestyle modification and Joint replacement

Analgesics

Weight loss

Joint replacement surgery



Kraakbeen topografie

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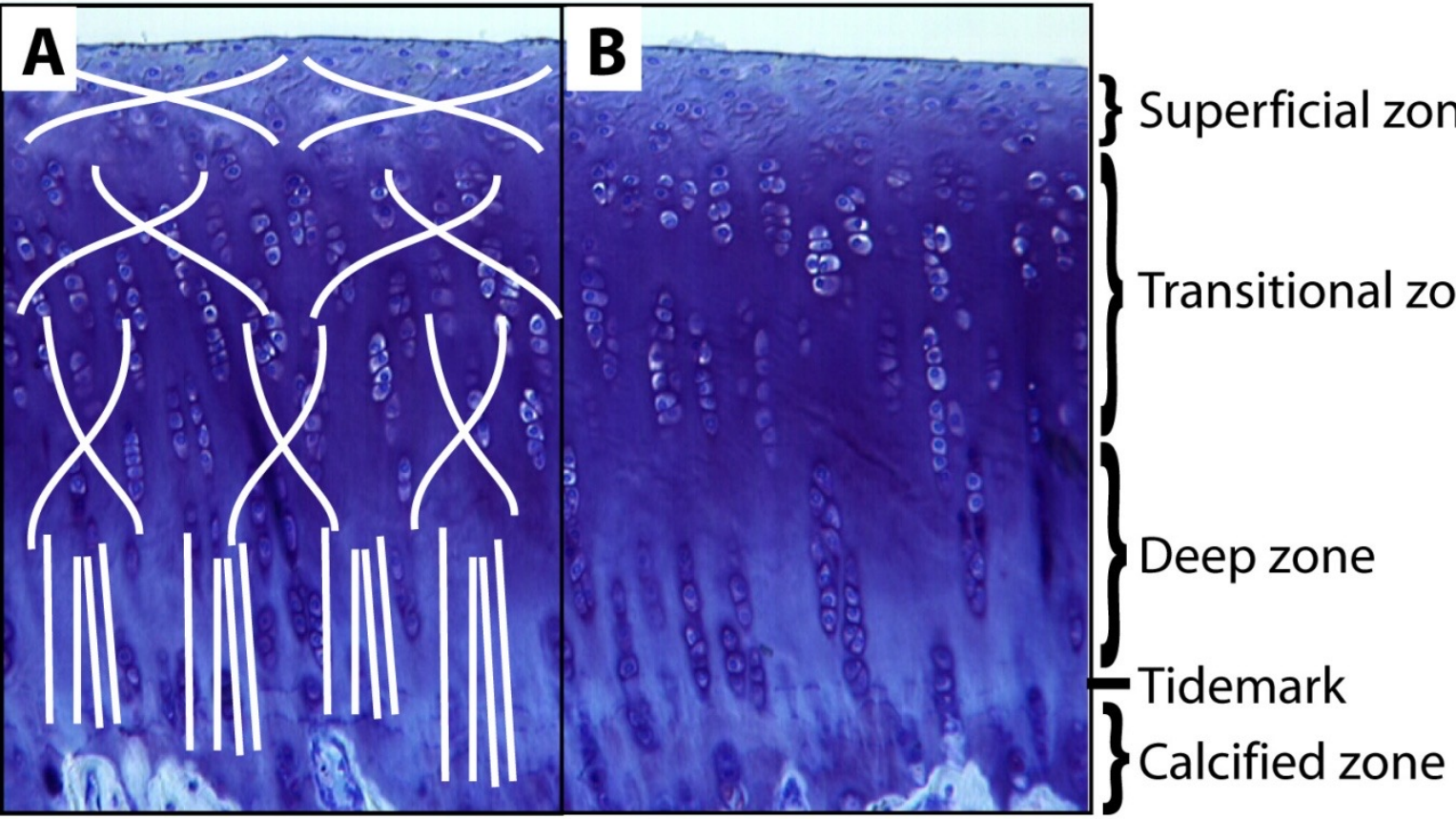

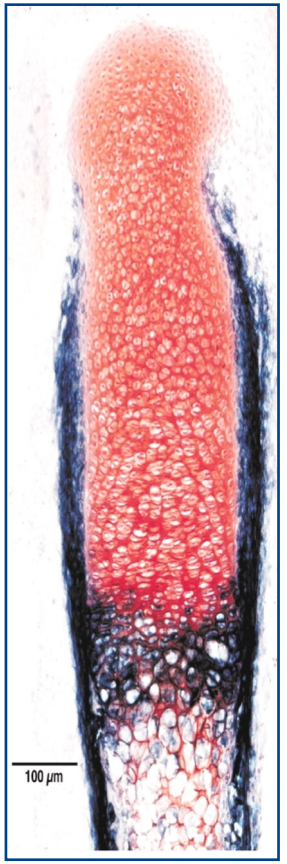

Kraakbeen defecten

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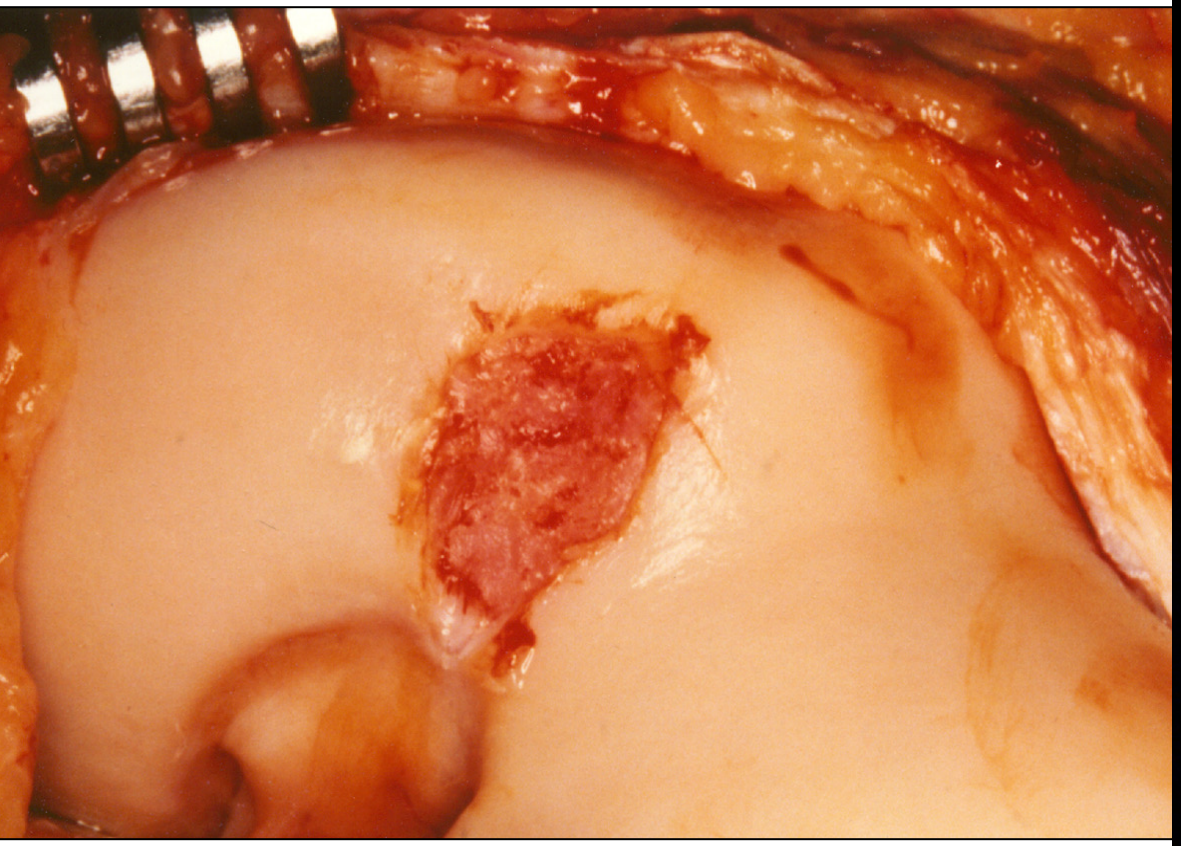
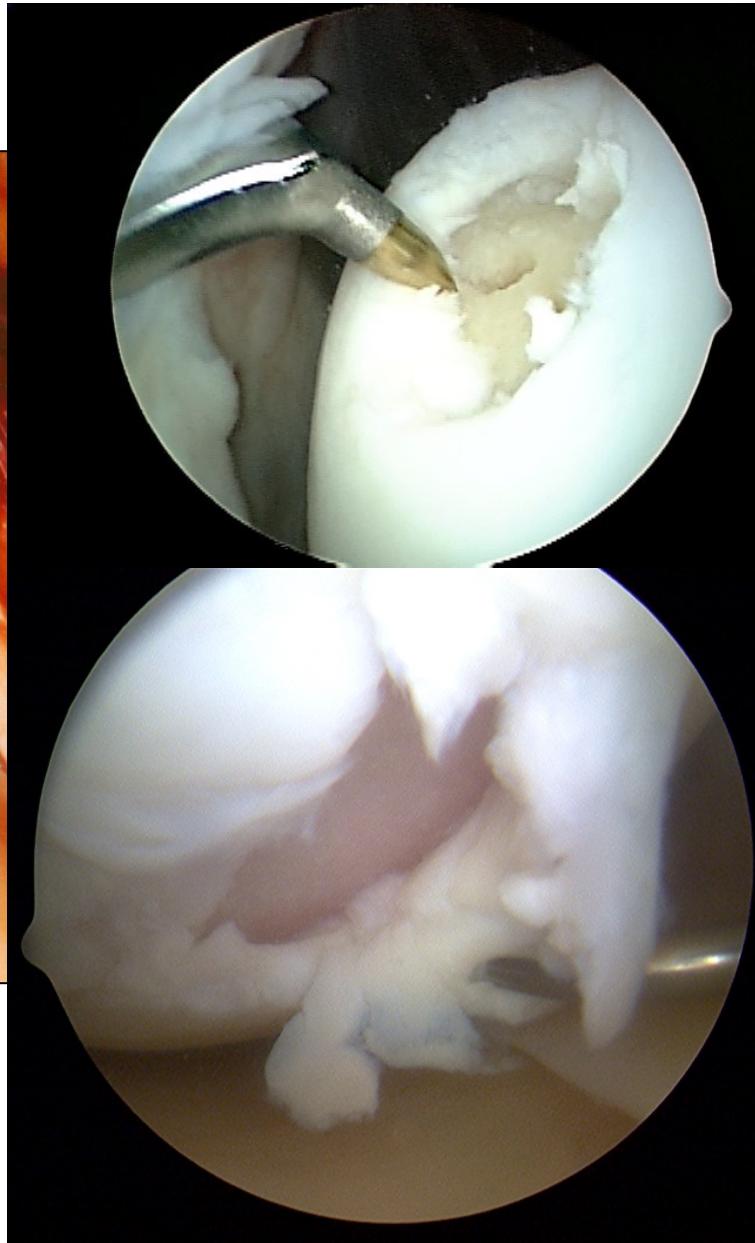
Het probleem





Kraakbeen reparatie technieken

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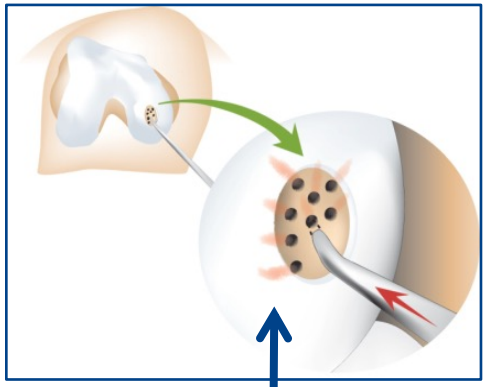
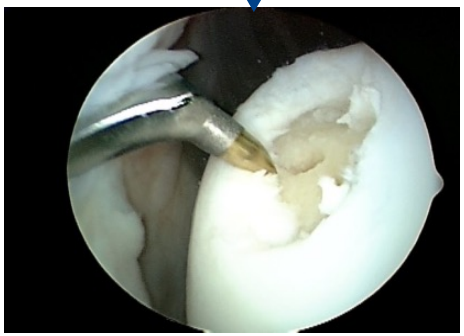
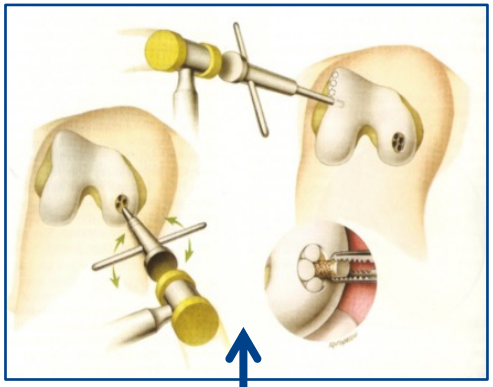
Aim Assesssment in clinical patients of performance, efficacy and safety of various (cellular) cartilage repair techniques with(out) use of T1-rho MRI imaging

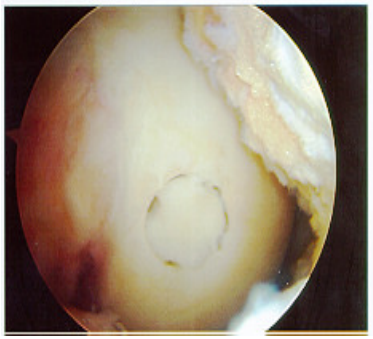
Microfracture



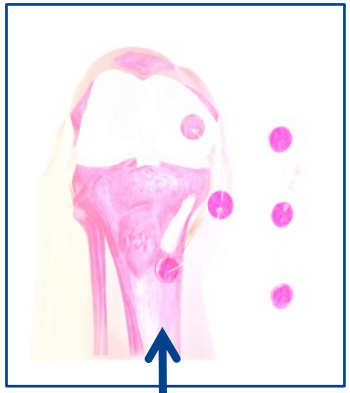


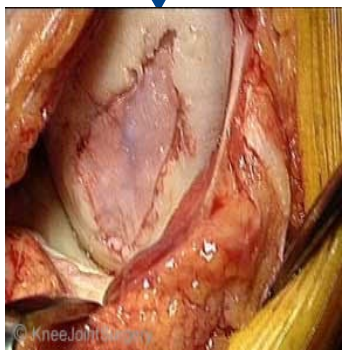
Mosaicplasty



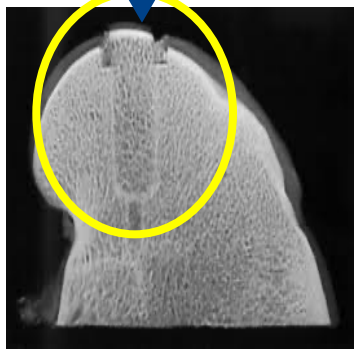


ACI/MACI





CaP plugs



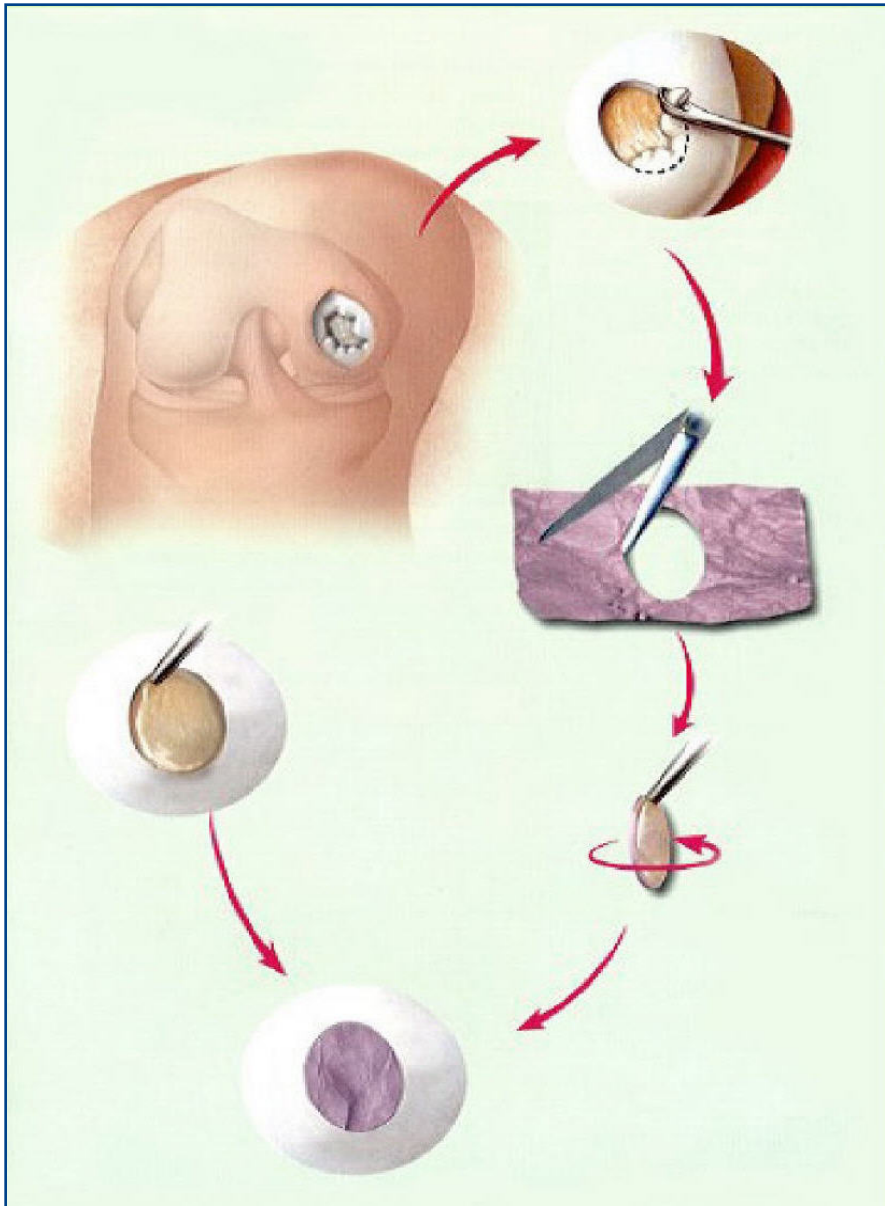
MACI Summit Trial Genzyme

- Operative technique
- Arthroscopy assessment of defect
- Randomisation 2 scenarios

B: Pt is MACI patient

- obtain a biopsy
- end surgery
- send biopsy to USA
- prepare MACI
- 6 weeks later implant MACI
- routine rehab protocol
  - * bracing
  - * CPM
  - * fysio

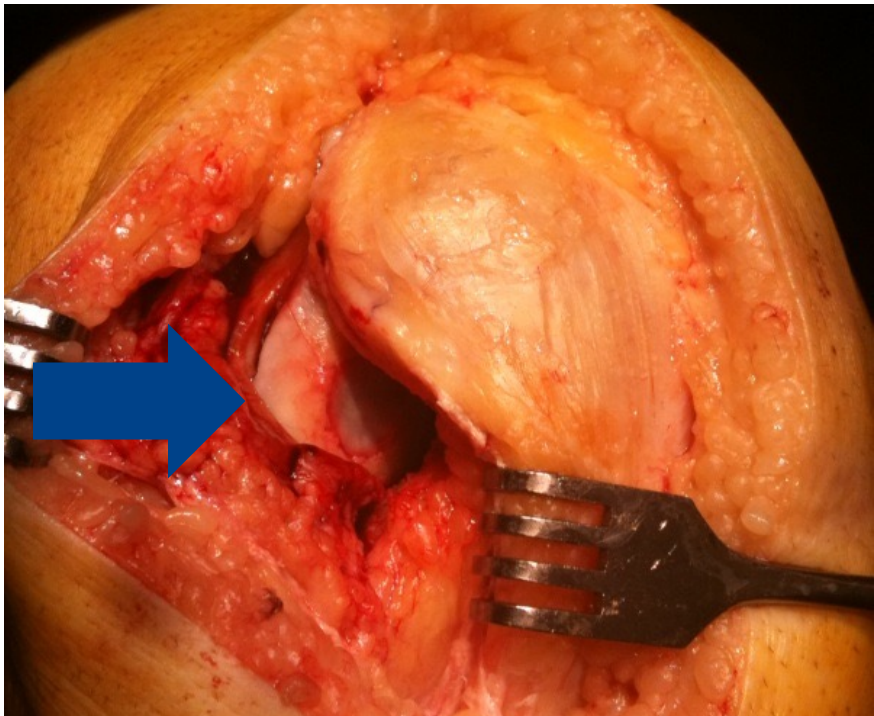
http://www.maci.com



Summit Trial Genzyme

Maastricht UMC+

- MACI implant
- collagen membrane 5 x 4 cm (20 cm2) in size
- 10-20 10^6 autologous chondrocytes (i.e.,$1x10^6$ cm^2)
- Trimmed to the size and shape of the cartilage defect and implanted
- Cell-side down into the defect.



Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Five-Year Follow-up of a Prospective Randomized Trial

Mats Brittberg,*† MD, PhD, David Recker,‡ MD, John Ilgenfritz,§ PhD, and Daniel B.F. Saris,*‖¶# MD, PhD, on behalf of the SUMMIT Extension Study Group**

Investigation performed by the SUMMIT Extension Study Group based on the multicenter study performed at 14 sites across 7 European countries

Background: Matrix-based cell therapy improves surgical handling, increases patient comfort, and allows for expanded indications with better reliability within the knee joint. Five-year efficacy and safety of autologous cultured chondrocytes on porcine collagen membrane (MACI) versus microfracture for treating cartilage defects have not yet been reported from any randomized controlled clinical trial.

Purpose: To examine the clinical efficacy and safety results at 5 years after treatment with MACI and compare these with the efficacy and safety of microfracture treatment for symptomatic cartilage defects of the knee.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: This article describes the 5-year follow-up of the SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) clinical trial conducted at 14 study sites in Europe. All 144 patients who participated in SUMMIT were eligible to enroll; analyses of the 5-year data were performed with data from patients who signed informed consent and continued in the Extension study.

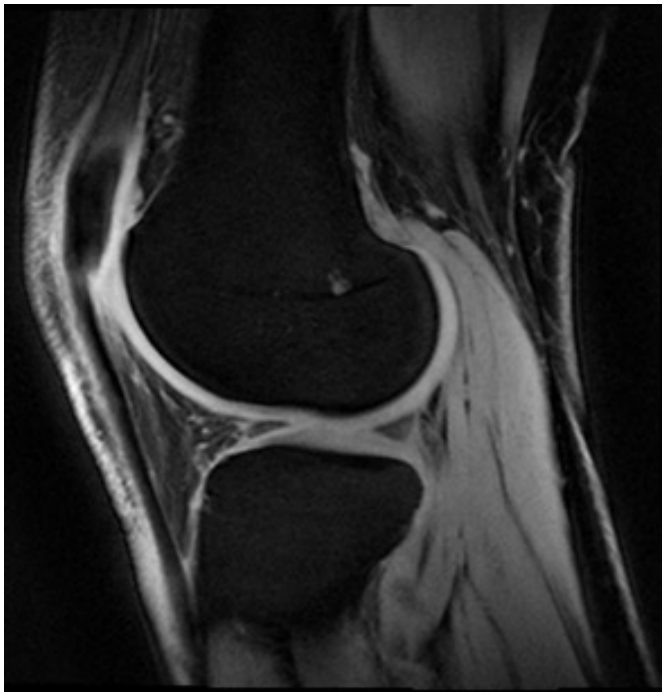
Results: Of the 144 patients randomized in the SUMMIT trial, 128 signed informed consent and continued observation in the Extension study: 65 MACI (90.3%) and 63 microfracture (87.5%). The improvements in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain and Function domains previously described were maintained over the 5-year follow-up. Five years after treatment, the improvement in MACI over microfracture in the co-primary endpoint of KOOS pain and function was maintained and was clinically and statistically significant ($P = .022$). Improvements in activities of daily living remained statistically significantly better ($P = .007$) in MACI patients, with quality of life and other symptoms remaining numerically higher in MACI patients but losing statistical significance relative to the results of the SUMMIT 2-year analysis. Magnetic resonance imaging (MRI) evaluation of structural repair was performed in 120 patients at year 5. As in the 2-year SUMMIT (MACI00206) results, the MRI evaluation showed improvement in defect filling for both treatments; however, no statistically significant differences were noted between treatment groups.

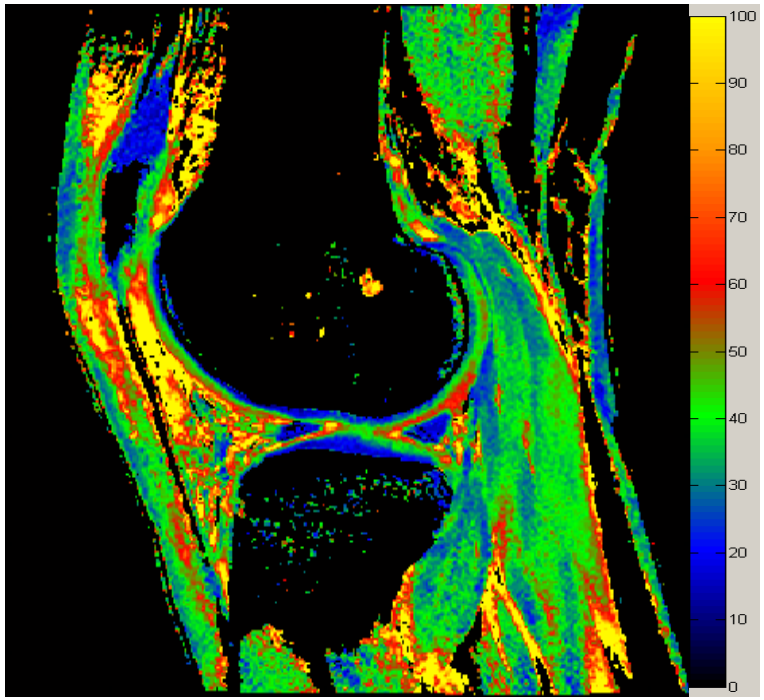
Conclusion: Symptomatic cartilage knee defects 3 cm^2 or larger treated with MACI were clinically and statistically significantly improved at 5 years compared with microfracture treatment. No remarkable adverse events or safety issues were noted in this heterogeneous patient population.

Keywords: cartilage repair; clinical outcomes; knee; matrix-applied characterized autologous cultured chondrocytes (MACI) implant; microfracture

T1rho MRI -> cartilage quality

- Meting water content, proteoglycanen content in kraakbeen
- Asessment OA en progressie van OA
- Semi-automatische kwantificatie ➔ longitudinale assessment mogelijk





vuistregel:

OA heeft oplopenede relaxatie tijden

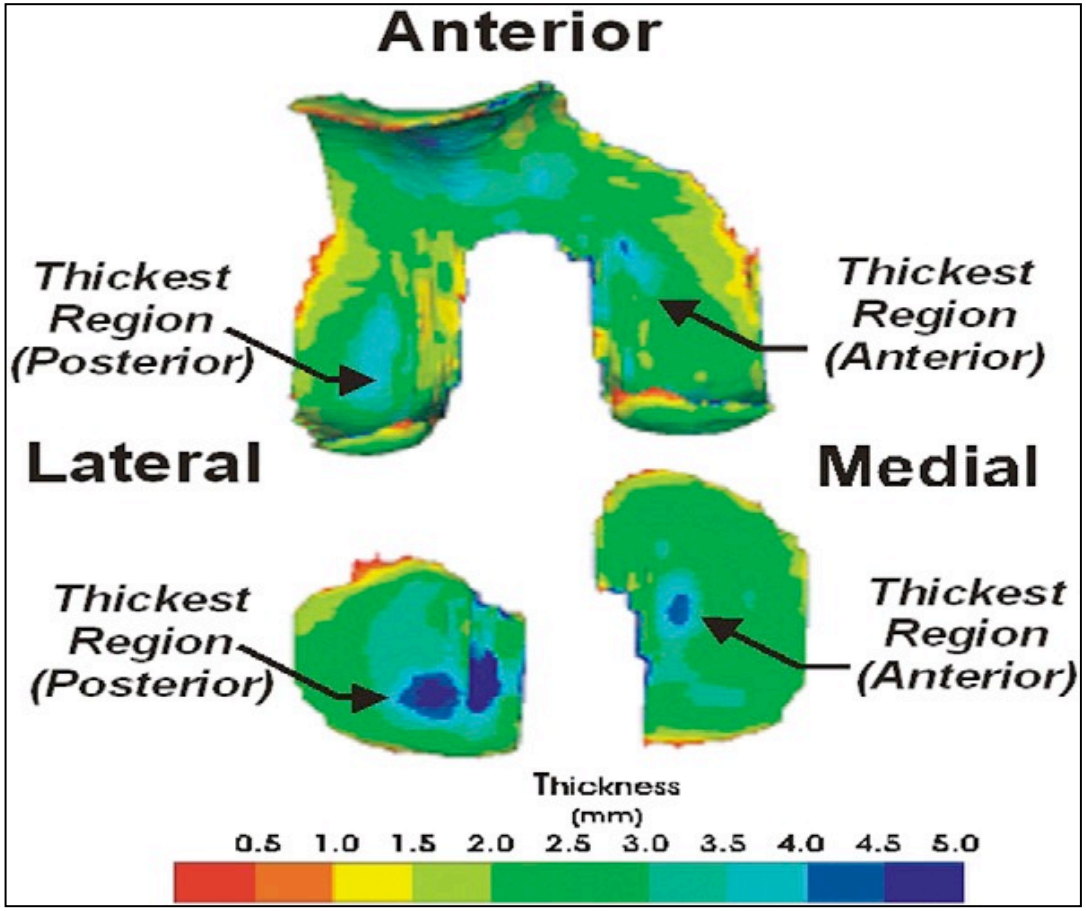
Geel is slechtere kraakbeen kwaliteit vergeleken met blauw

T1rho relaxation map of a healthy subject

- Wang L et al. T1rho MRI of menisci and cartilage in patients with osteoarthritis at 3T. Eur J Radiology 81:2329-36, 2012
- Menezes MN et al. T2 and T1rho MRI in articular cartilage systems. Magn Reson Med 51(3):503-9, 2004.

T1rho MRI -> kraakbeen kwaliteit

- **Kwantificatie kraakbeen dike ➔ longitudinale assessment mogelijk**



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7 Tesla MRI -> kraakbeen kwaliteit

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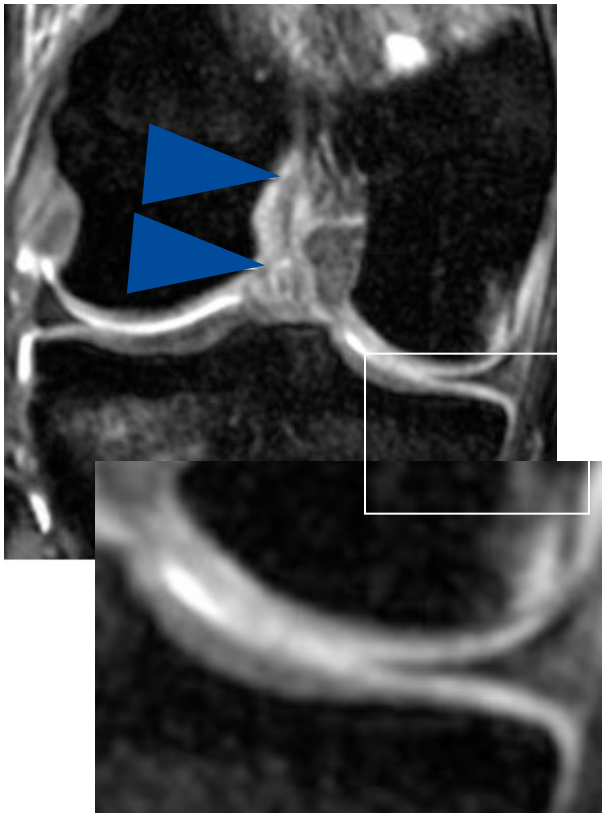
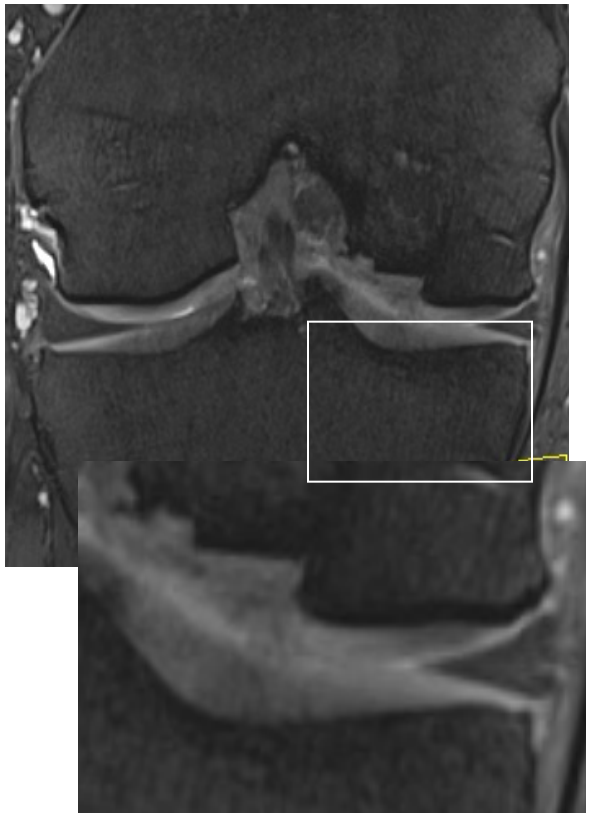
- Maastricht Scannexus 9.8 and 7.0 Tesla MRI

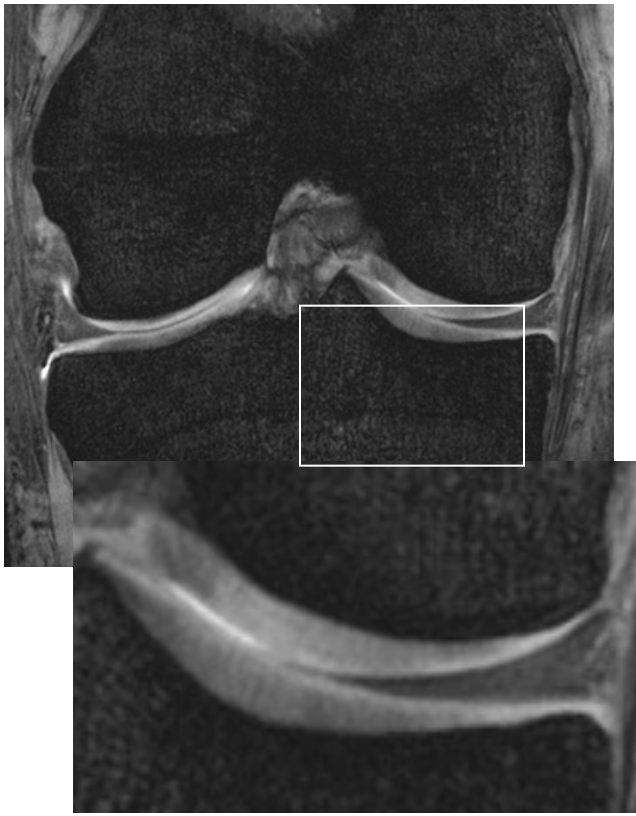
1.5 Tesla



3.0 Tesla



7.0 Tesla



7 Tesla MRI -> kraakbeen kwaliteit

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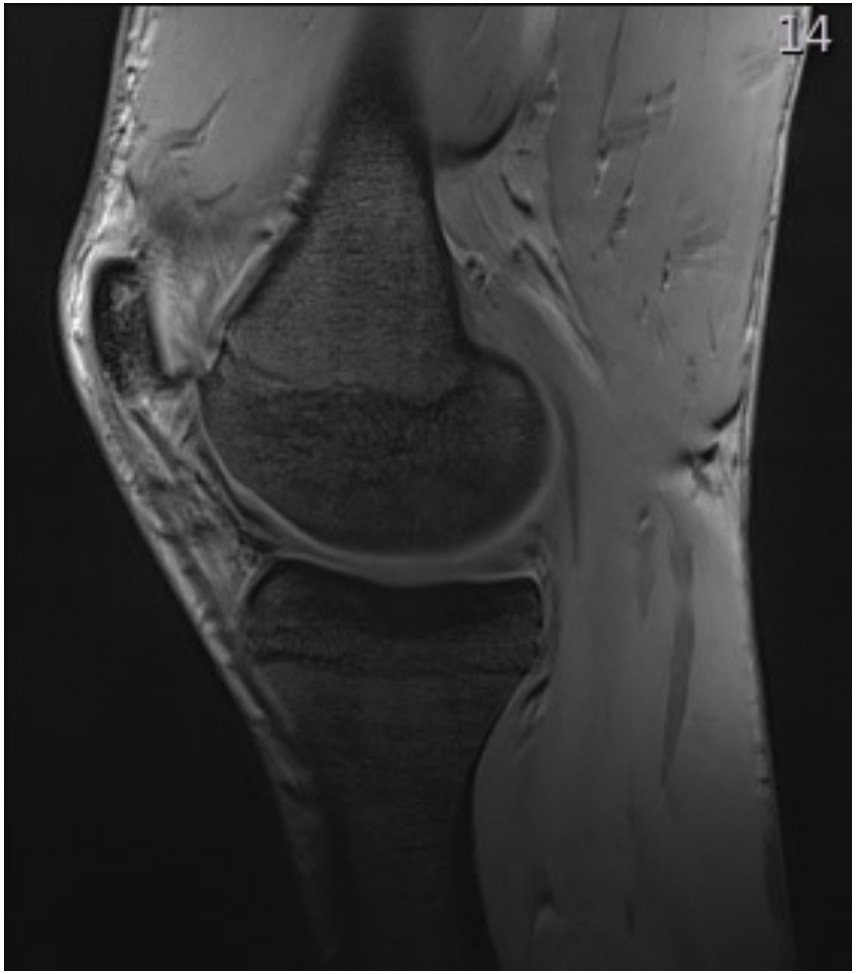
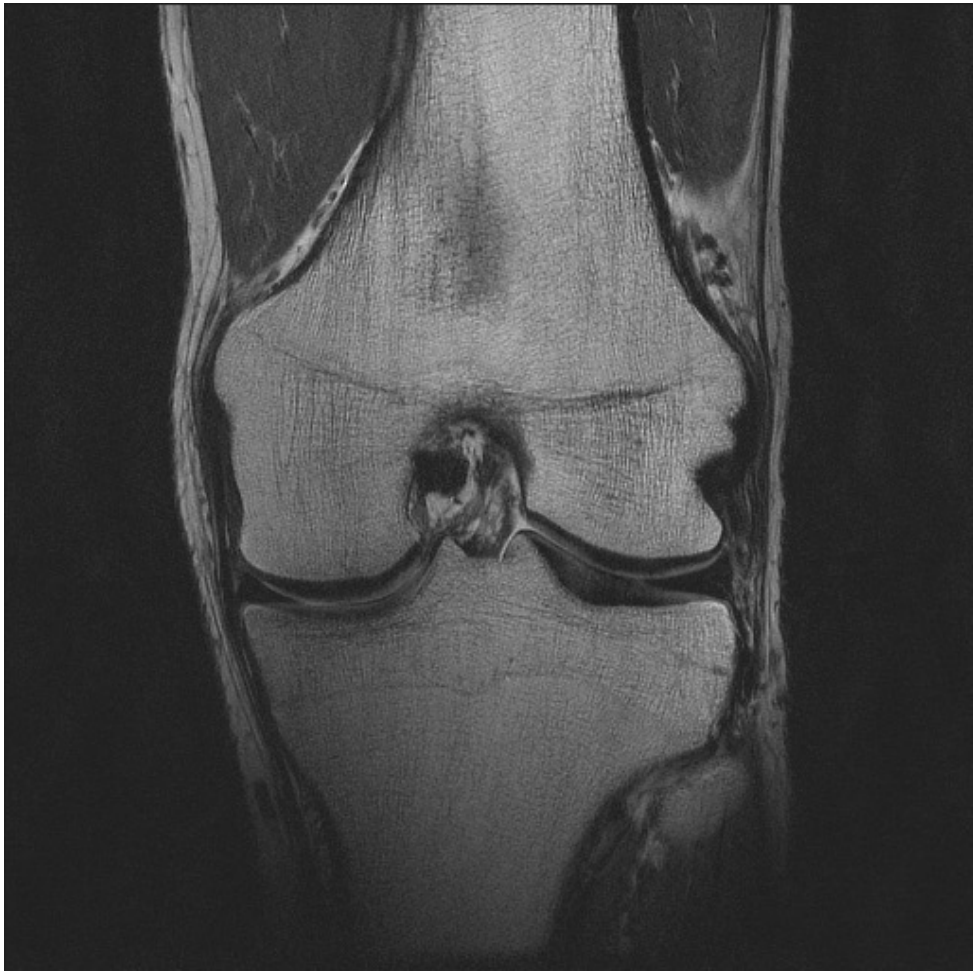
- 7 Tesla MRI Maastricht





ATMPs

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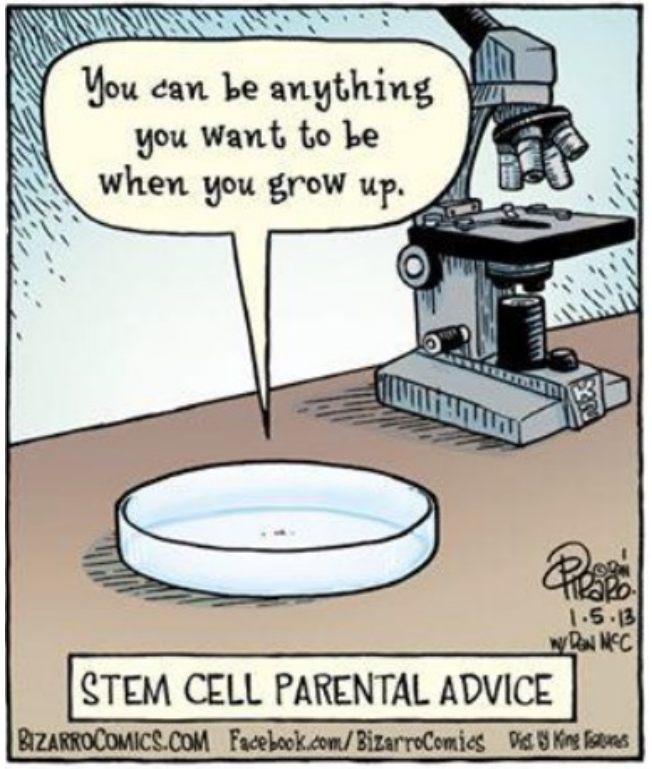
Advanced therapies Medicinal products

- Medicinal products based on cells or genes
- Very different from medicines based on chemical entities or biological /biotechnological origin
- Same requirement for testing /controlling each batch

Typen

1. Gene therapy medicinal products
2. Somatic cell therapy medicinal products
3. Tissue engineering products
4. Tumor cells



ATMPs

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1. Gene therapy medicinal products (n=12)

- introduction or re-introduction of whole human cells (normal or modified) to generate an immune response in patients with deficient immunity

2. Somatic cell therapy medicinal products (n=3)

- introduction of normal or modified genetic material (usually DNA) into a patient to alleviate a genetic deficiency

3. Tissue engineering products (n=10)

- the manipulation/growth of biological tissue for implantation/use on tissue deficient patients.

Paul-Ehrlich-Institut

Federal Institute for Vaccines and Biomedicines

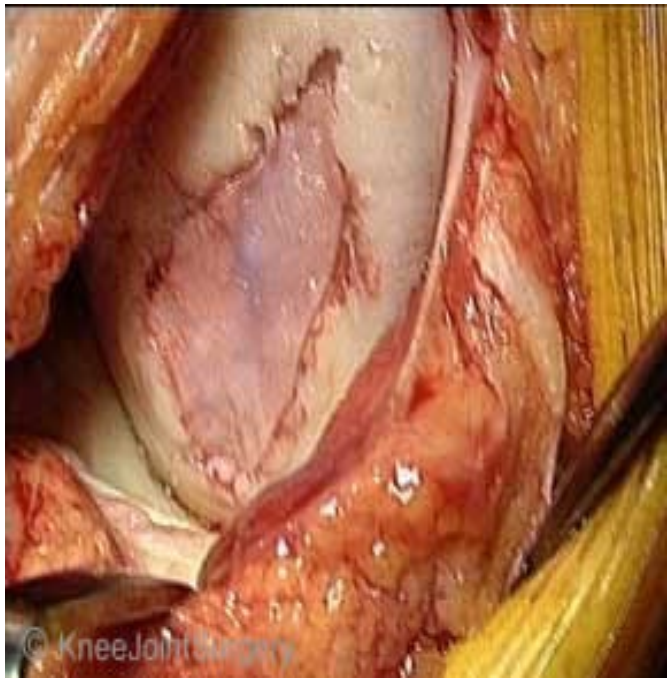
Maastricht UMC+

3. Tissue engineering products

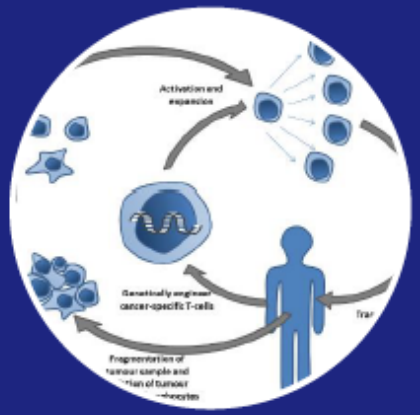
Paul-Ehrlich-Institut

Federal Institute for Vaccines and Biomedicines

- BioSeed-C Autologes 3D-Chondrozytentransplantat,
- Chondrosphere,
- MACI, Genzyme Europe
- NOVOCART 3D / NOVOCART Inject
- t2c001, autologous bone marrow-derived progenitor cells

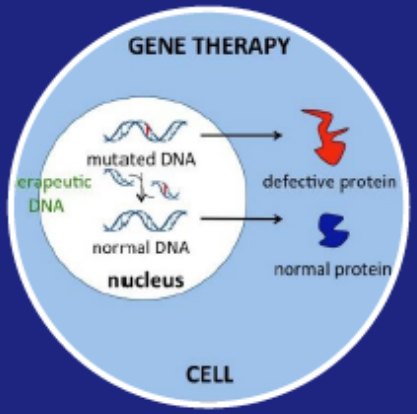


Cell Therapies



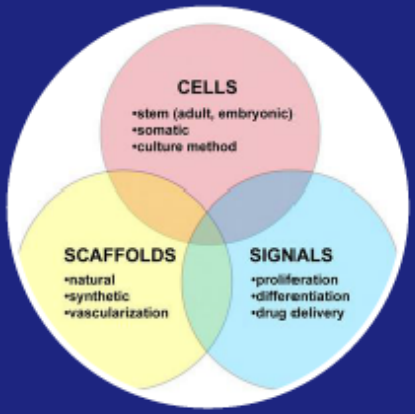
Cell Therapies

- Melanoma, Leukaemia, Lymphoma
- Mostly B-Cell
- More treatments in develpment



Gene Therapies

- Haemophilia, Cystic Fibrosis, Muscular Dystrophy, some imminodeficiences
- More treatments in development



Engineered Tissue

- Cartilage
- Corneas
- Bone
- More treatments in development

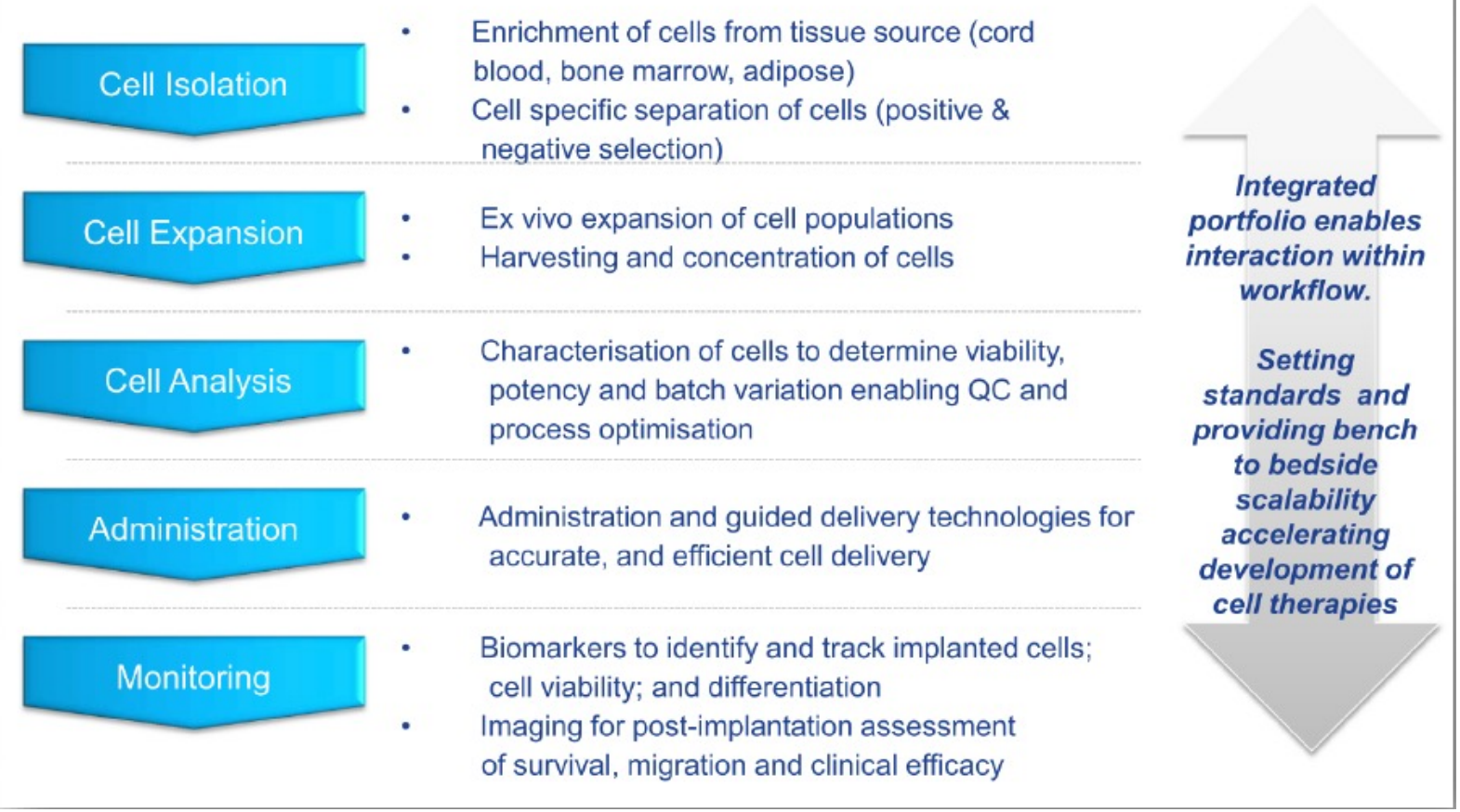
Why are they important?

ATMPs are showing outstanding results in difficult to treat conditions

- Personal, customised medicines, providing next level breakthroughs
- Gene therapies showing promise in repairing/curing genetic disorders
- Cell therapies able to target and destroy disease cells while minimising damage to healthy cells
- Engineered tissue repairing tissue that the body is unable to repair naturally – cartilage, corneas, etc.

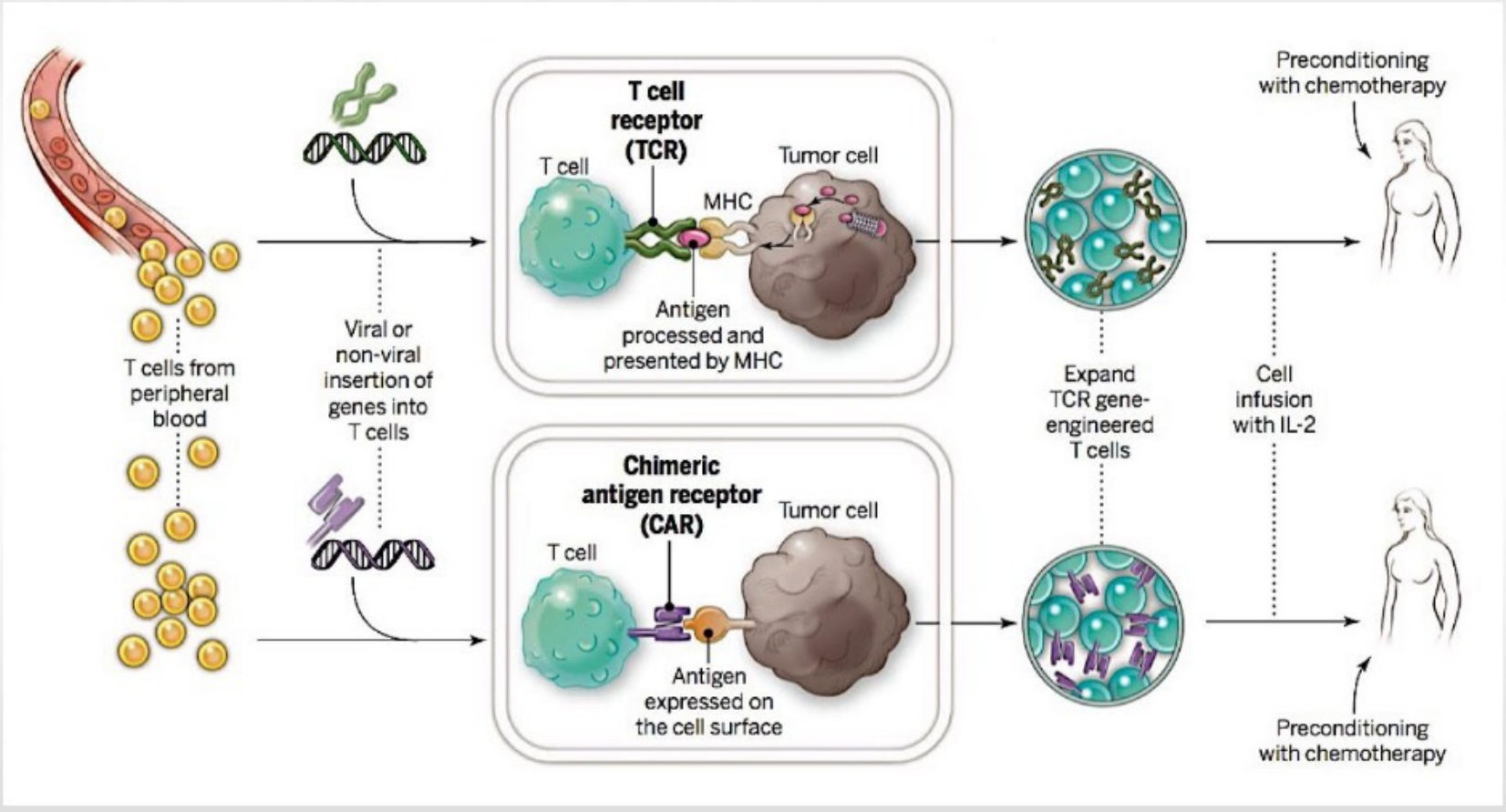
How do you make them?

Cell Therapy Generic Workflow



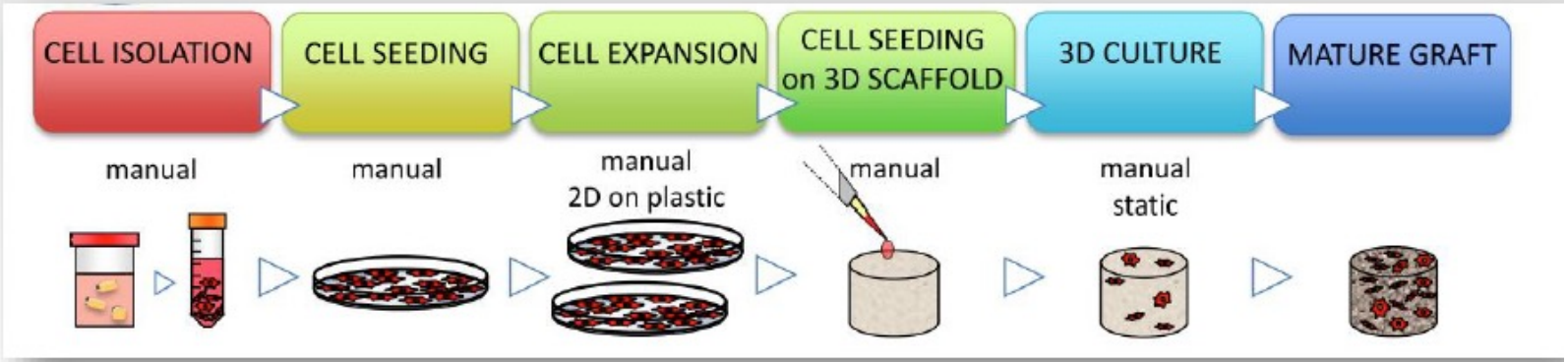
How do you make them?

Typical CAR-T/TCR-T cell therapy process

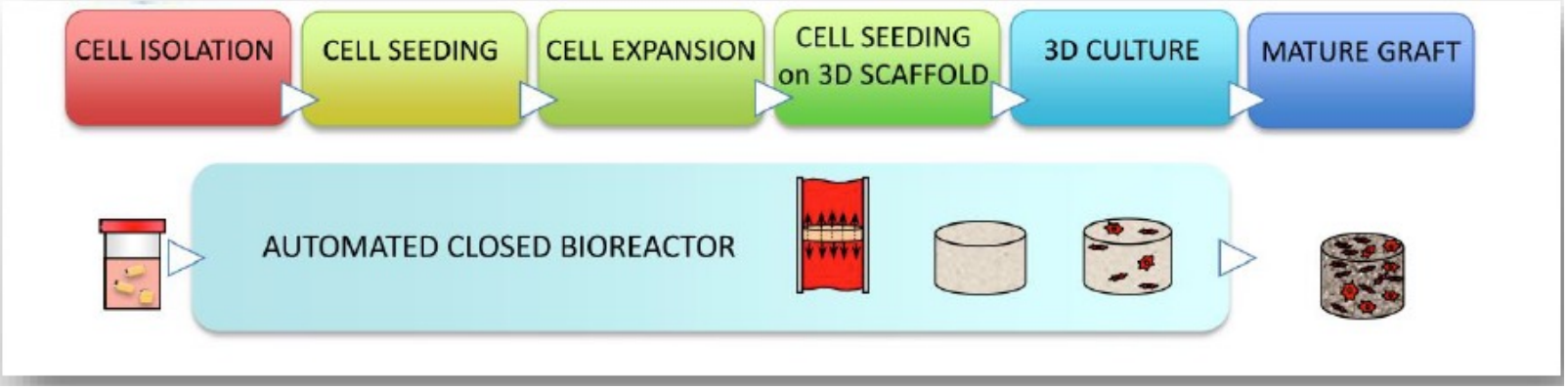


How do you make them?

Typical manual engineered tissue process



Near future automated engineered tissue process



GMP Production or Clinical Trials?

Currently, the vast majority of ATMPs developed are in clinical trials. Many are in extended (seemingly perpetual) clinical trials. Why?

- Applying GMP is difficult
- Getting MA is very difficult
- Establishing a reimbursement model that works commercially remains a major concern

MDR -> Medical device regulation

Maastricht UMC+

From Medical Device Directive -> Medical Device Regulation
Into effect May 26th 2021

European Commission

Medical Devices Regulation

EU MDR

MDR -> Medical device regulation

Maastricht UMC+

From Medical Device Directive -> Medical Device Regulation
Into effect May 26th 2021

Een antimicrobieele coating

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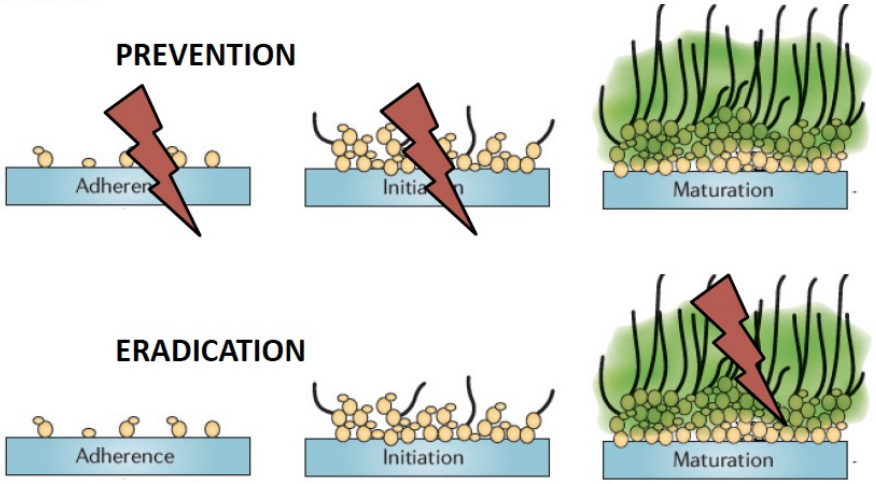
Dartbac antimicrobieele technology ontwikkeling

dartbac



Welke eigenschappen moeten we testen en conform welke regel- en wetgeving of industrie standaarden?

Example: antimicrobial coating

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Dartbac antimicrobial technology development

dartbac

	In vitro	*In vivo*	*Clinical study*
Biocompatibility assessment	ISO 10993	ISO 10993	ISO 14155 / GCP
	ASTM	ASTM	
Antimicrobial properties assessment	ISO 22196	ISO 22196	ISO 14155 /GCP
	JIS Z2801	JIS Z2801	
	ASTM	ASTM	
Clinical efficacy assessment	ISO 10993	ISO 22196	ISO 14155 GCP
	ASTM	JIS Z2801	

Notified Bodies

FDA

EMA

AOP adverse outcome pathways

ISO 13485

QA & RA expertise industry partners

MDR

Introductie

Design-ontwikkel fase
- gebruiker eisen
- ontwikkel input, proces, validatie

Technische file fase
- device beschrijving
- conformity -> CE
- label en IFU
- technische standaarden
- lab reusltaten
- klinische data

* RISICO ANALYSE !
* KWALITEITS ANALYSE !

Risico analyse fase
- Harm/hazard/hazardous situation
- deel van technische file

Klinisch onderzoek fase
- veiligheid en effectiviteit
- post-marketing follow-up

MDR -> Medical device regulation

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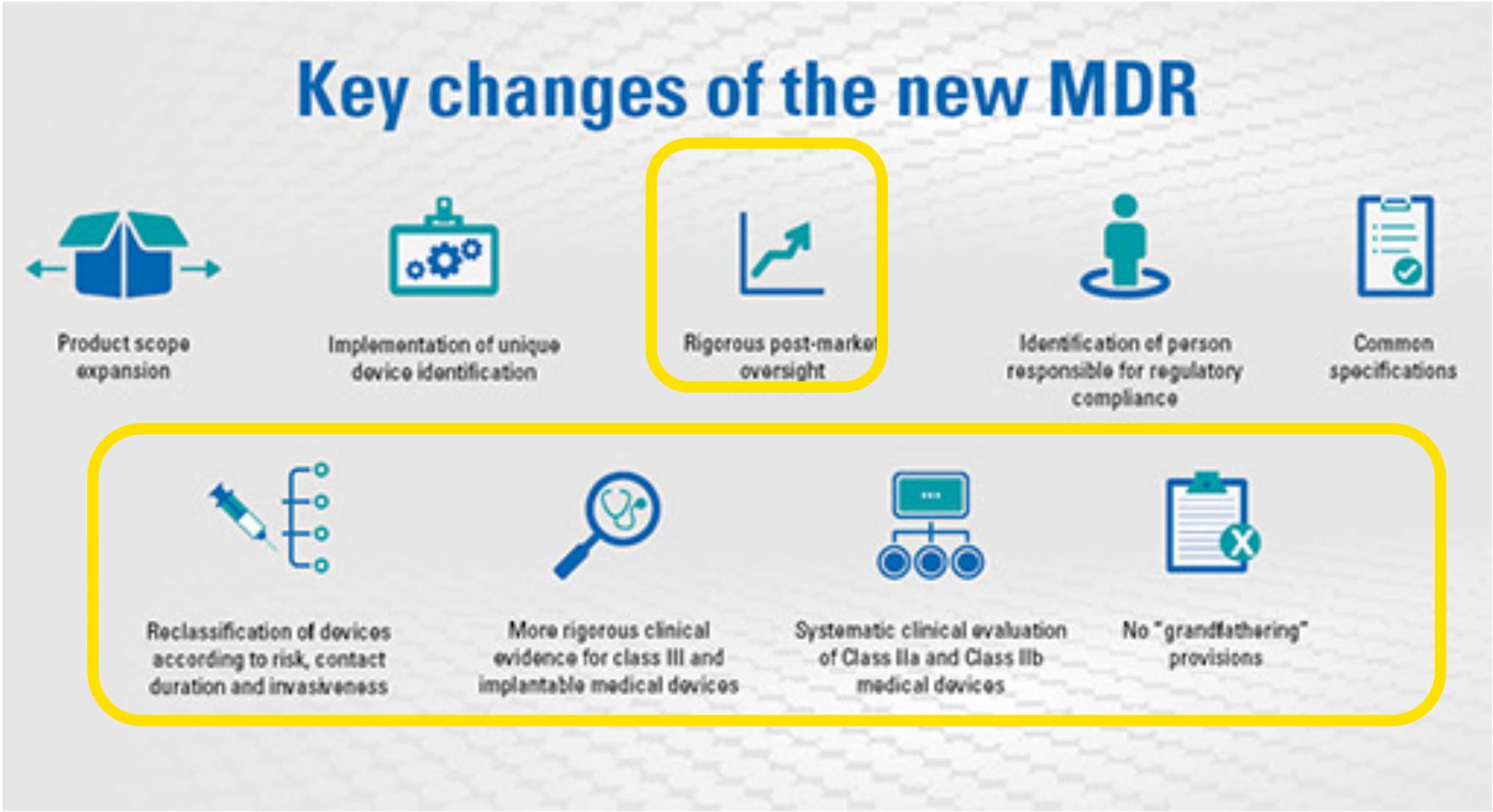

Classificatie -> risico, contactduur en invasiviteit

MDR -> Medical device regulation

Maastricht UMC+

1. **Re-classificatie alle medical devices / biomaterialen**

2. **Re-evaluatie technische dossiers alle medical devices / biomaterialen**
   - Zelf gegenereerde productspecifieke unieke data productveiligheid, effectiviteit

Exeter ≠ **Trilliance** **Alteon** **C-stem** **Hype**

3. **Doorlopende risico evaluatie alle medical devices / biomaterialen, ATMPs**

4. **Verplichte post-marketing surveillance en jaarlijkse rapportage**

Risico analyse

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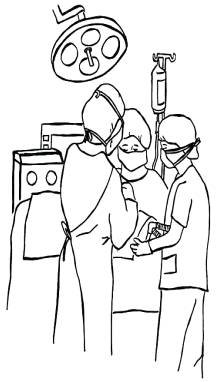
Hazard
Gevaar

Hazard

Hazardous Situation
Gevaarlijke situatie

Hazardous situation

Harm
Schade



Harm

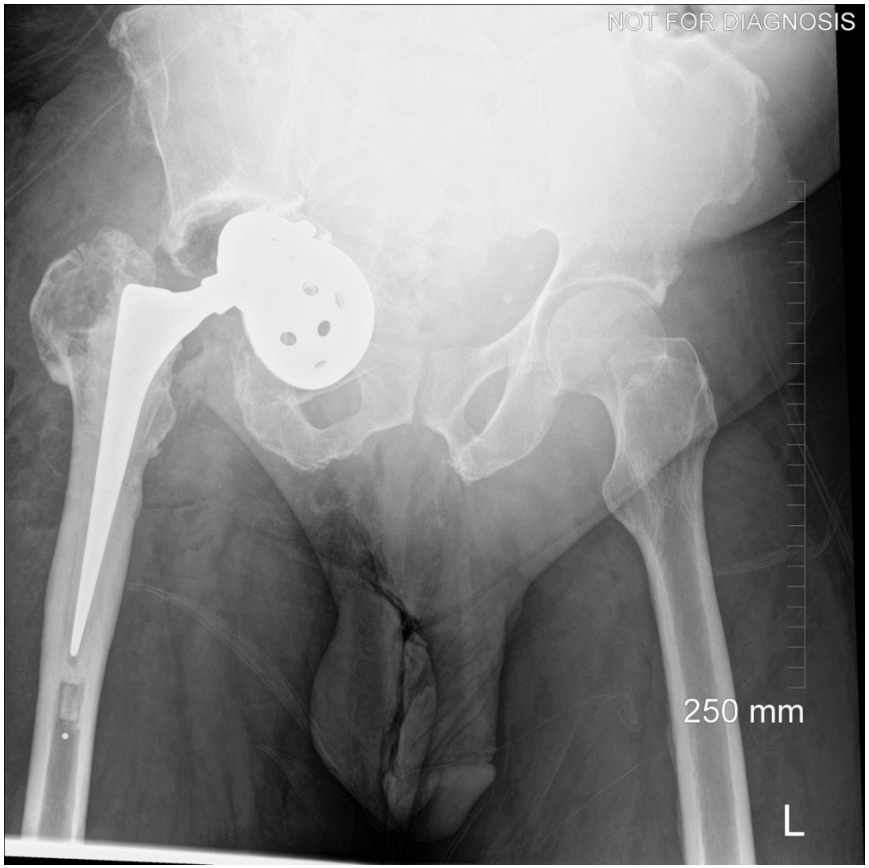
Hazard: Potential source of harm (failure mode)

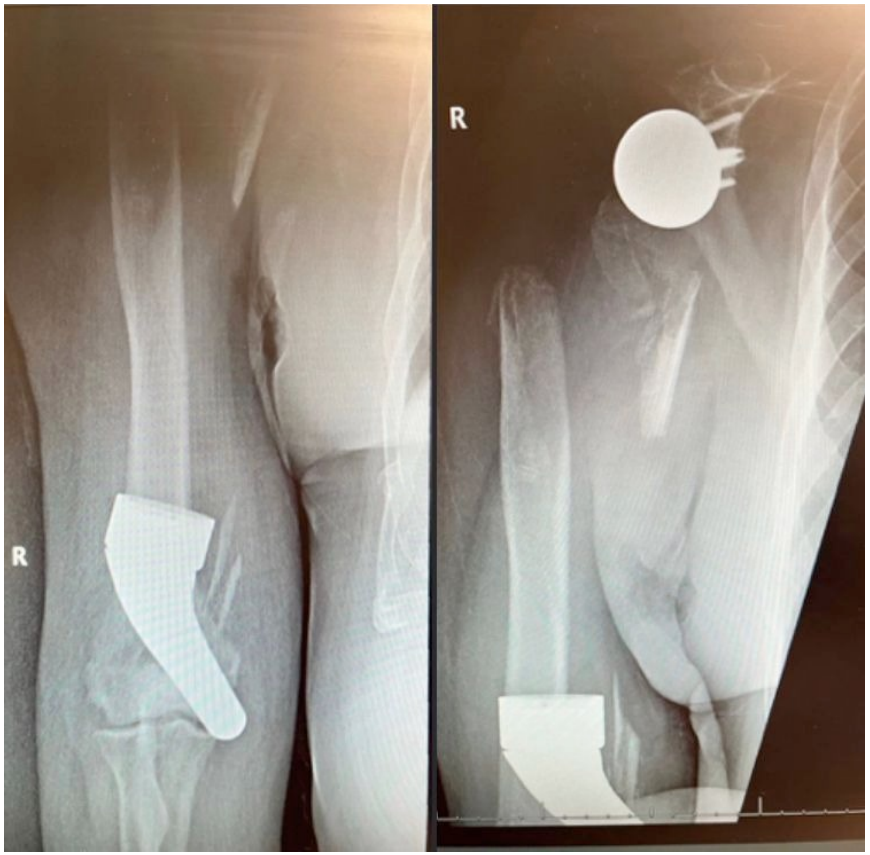
Harm: physical injury or damage to the health of people, or damage to property or the environment

Hazardous situation: Circumstance with exposure to harm

Risk: Combination of the severity of harm and the probability of occurrence of that harm.

Risico analyse





Conclusies

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Effect van de MDR -> Medical Device Regulation

- MDR heeft een enorm effect op de huidige medical devices en biomaterialen markt en de toekomstige biomaterialen ONTWIKKELING en GOEDKEURING

- Vereisten:
  - Unieke zelf gegenereerde data betreffende veiligheid (safety) en klinische effect (clinical efficacy) voor re-certificatie en markt herintreding voor elk medical device en biomateriaal
  - Evaluatie kwantiteit en kwaliteit van level of evidence
  - Verplichte post-marketing surveillance en risico-inventarisatie gedurende product levenscyclus & SAE rapportage

- MDR zal hierdoor leiden tot een drastische reductie van beschikbare medical devices (-60%) en biomaterialen (-40%)

- MDR heeft een enorm effect op de toekomstige opzet van klinisch onderzoek met vergaande focus op veiligheid en risico inventarisatie en SAE reportage

Conclusies

Maastricht UMC+

Positief effect van de MDR -> Medical Device Regulation

- Implantaten -> hogere LoE beschikbare implantaten
  -> beter veiligheidsprofiel vanwege continu risico analyse
  -> specifiekere training en educatie vanuit industrie
  -> EU breed track & trace

- Klinisch onderzoek
  -> belang neemt toe !
  -> vereist tijdens gehele levenscyclus implantaat
  -> post-marketing surveillance vereist inclusief risico analyse
  -> belang implantaat registers neemt toe

- Personalised / patient specieke implantaten
  -> wetgeving en eisen nog onduidelijk
  -> geen status aparte op moment
  -> even strigente klinsche follow-up eisen

Questions