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# **OSTEONECROSI DEI MASCELLARI ASSOCIATA AI BIFOSFONATI: PREVENZIONE E VALUTAZIONE DEL RISCHIO**

## **Linee Guida, Raccomandazioni e Prospettive Future**

# 1. RAZIONALE

- Ipotesi tradizionale: chirurgia e infezioni odontostomatologiche fattore di rischio primario
- Letteratura (2003-2007): “Interventi chirurgici/infezioni (estrazioni, impianti, parodontite etc.) precedenti l’insorgenza dell’ONJ sono riportati dal 70-80% dei pazienti”

## INCIDENCE AND RISK FACTORS OF BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS

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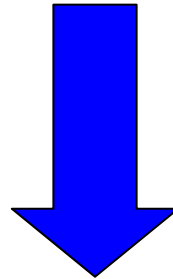
ORIGINAL REPORT

## Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates: Incidence and Risk Factors

Aristotle Bamias, Efstathios Kastritis, Christina Bamia, Lia A. Mouloupoulos, Ioannis Melakopoulos, George Bozas, Vassiliki Koutsoukou, Dimitra Gika, Athanasios Anagnostopoulos, Christos Papadimitriou, Evagelos Terpos, and Meletios A. Dimopoulos

# 1. RAZIONALE

- Razionale: Prevenzione/riduzione del rischio possibile se si eliminano i fattori di rischio primario (chirurgia e infezioni odontostomatologiche)



## **Recommendations for the management of patients on bisphosphonate therapy.**

N.B. (Includono anche raccomandazioni generali su safety e feasibility delle procedure odontoiatriche)

## 2. LIVELLO DI EVIDENZA

- Non esistono studi che supportino **NESSUNA** delle attuali raccomandazioni con un sufficiente livello di evidenza.
- Non esistono linee guida EBM
- Raccomandazioni sono basate su “Expert Opinions”.
- Molteplici differenze e controversie



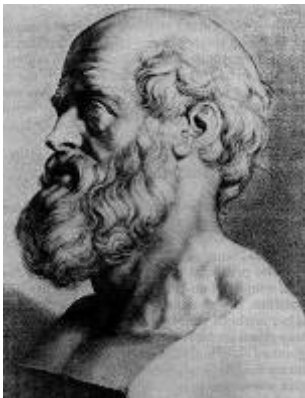
### 3. RACCOMANDAZIONI

- American Dental Association
- European Myeloma Network
- Advisory Group of the Myeloma Foundation of Australia
- Canadian Association of Oral and Maxillofacial Surgeons
- International Expert Panel
- American Society for Bone and Mineral Research
- American Academy of Oral Medicine
- American Academy of Oral & Maxillofacial Surgeons
- ANDI-SIOMMMS
- etc. etc.



### 3. RACCOMANDAZIONI : revisione critica della letteratura (Fedele S et al. Oral Diseases 2009, *in print*)

- Valutazione del razionale scientifico
- Valutazione del grado di evidenza
- In assenza di evidenza, conclusioni basate sul principio del “Clinically sensible and non detrimental”



*Primo non nocere*

## 4. RISULTATI

### 1a. Raccomandazioni (Oral BP)

- Pazienti già esposti ai BP
- Pazienti che saranno esposti ai BP

### 1b. Strategie di identificazione/riduzione del rischio chirurgico

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### 2a. Raccomandazioni (i.v. BP)

- Pazienti già esposti ai BP
- Pazienti che saranno esposti ai BP

### 2b. Strategie di identificazione/riduzione del rischio chirurgico

## Critical review of dental recommendations with respect to oral BP therapy - 1

<b>Dental treatment to provide</b>	<b>Individuals due to start oral BP</b>		<b>Individuals receiving oral BP</b>	
	<b>Recommendation/Comment</b>	<b>Level of evidence</b>	<b>Recommendation/Comment</b>	<b>Level of evidence</b>
Restorative	Safe. Consider surgical alternatives for teeth with poor-prognosis. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Safe. Consider non-restorative alternatives for teeth with poor-prognosis. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.
Endodontic (non surgical)	Safe. Consider surgical alternatives for teeth with poor-prognosis. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Likely safe. Insufficient evidence to suggest that root canal treatment may trigger BOJ. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.
Surgery (including endodontic surgery and implants)	Safe. Time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low. But recommendation is clinically sensible.	Relatively safe. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection but may trigger BOJ itself. The small risk of BOJ does not contraindicate surgical procedure.	Low. But recommendation is clinically sensible. No evidence to support any of the suggested risk-reduction strategies (see table 3).

## Critical review of dental recommendations with respect to oral BP therapy - 2

Periodontology	<p>Safe.</p> <p>In case of periodontal surgery, enough time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p>	<p>Relatively safe.</p> <p>It may help reducing the risk of BOJ <i>via</i> prevention of bone infection but periodontal bone surgery may trigger BOJ itself. The small risk of BOJ does not contraindicate periodontal surgery.</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p> <p>No evidence to support any of the suggested risk-reduction strategies (see table 3).</p>
Prosthetic	<p>Safe.</p> <p>Mucosal trauma should be avoided where possible</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p>	<p>Likely safe.</p> <p>Mucosal trauma should be avoided where possible</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p>
Orthodontics	<p>Safe.</p> <p>Enough time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible.</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p>	<p>Likely safe.</p> <p>Some studies reported slow/ impaired tooth movements. No evidence to support the theory that increased turn-over can cause further accumulation of BP into the alveolar bones and trigger osteonecrosis.</p>	<p>Low.</p> <p>But recommendation is clinically sensible.</p>

## Strategie di identificazione/riduzione del rischio chirurgico – oral BP

<i>Strategy</i>	<i>Description</i>	<i>Comment</i>
Evaluation of CTX levels and potential discontinuation of BP	CTX > 150 pg/mL: low risk, surgery safe	Not supported by any evidence
	CTX < 150 pg/mL: high risk. Defer surgery, plan drug holiday and wait for CTX to rise.	
Discontinuation of oral BP	Discontinuation of oral BP for 1-3 months before surgery +/- 3 months after.	Not supported by any evidence
Sextant-by sextant approach	Applies to cases where surgery is planned in multiple quadrants. Treat one quadrant first, and wait 2 months. In case of normal healing and no osteonecrosis, multiple-quadrant treatments can be provided safely at once.	Not supported by any evidence but non-harmful and clinically sensible.
Conservative surgical techniques	E.g. primary tissue closure	Not supported by any evidence but non-harmful and clinically sensible.
Topical antimicrobials	Chlorhexidine before, during and up to 2 months after surgery.	Not supported by any evidence but non-harmful and clinically sensible.
Systemic antibiotics	In case of extensive surgical manipulation of the bone, use of prophylactic systemic antibiotics may be considered by the clinician, also depending on the presence of concomitant factors (abscess, acute infection, other therapies etc.). A regimen of amoxicillin +/- metronidazole or clindamycin for 2 days before and 14 days after surgery has been suggested.	Not supported by any evidence. Potentially harmful due to the risk of antibiotic resistance and potential allergic reactions
Alternative extraction techniques	Elastic-induced gradual orthodontic tooth exfoliation. An elastic (orthodontic) band is placed around the cervical part of the tooth to induce extrusive movement in 1-3 months (mean 6 weeks). Separation of the roots, endodontic therapy and regular grounding of the crown is required.	Potentially effective but data are from one case series without controls. Time-consuming and inadequate in case of acute infection.

## Critical review of dental recommendations with respect to iv BP therapy - 1

<b>Dental treatment to provide</b>	<b>Individuals due to start iv BP</b>		<b>Individuals receiving iv BP</b>	
	<b>Recommendation/Comment</b>	<b>Level of evidence</b>	<b>Recommendation/Comment</b>	<b>Level of evidence</b>
Restorative	Safe. Consider surgical alternatives for teeth with poor-prognosis. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low, but recommendation is clinically sensible.	Safe. Consider non-restorative alternatives for teeth with poor-prognosis. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection.	Low, but recommendation is clinically sensible.
Endodontic (non surgical)	Safe. Consider surgical alternatives for teeth with poor-prognosis. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low, but recommendation is clinically sensible.	Likely safe. Insufficient evidence to suggest that root canal treatment may trigger BOJ. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection.	Low, but recommendation is clinically sensible.
Surgery (including endodontic surgery and implants)	Safe. Time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible. It may help preventing BOJ <i>via</i> prevention of bone infection.	Low, but recommendation is clinically sensible.	Contraindicated. When surgery can not be avoided, there are risk-reduction strategies and alternative techniques to consider (see table 5).	Significant evidence that oral surgery is contraindicated.

## Critical review of dental recommendations with respect to iv BP therapy - 2

Periodontology	<p>Safe.</p> <p>In case of periodontal surgery, enough time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible.</p> <p>It may help preventing BOJ <i>via</i> prevention of bone infection.</p>	Low, but recommendation is clinically sensible.	<p>Non-surgical therapy is likely to be safe. It may help reducing the risk of BOJ <i>via</i> prevention of bone infection</p> <p>Surgical therapy is contraindicated.</p>	Significant evidence that periodontal surgery is contraindicated.
Prosthetic	<p>Safe.</p> <p>Mucosal trauma should be avoided where possible</p>	Low, but recommendation is clinically sensible.	<p>Likely safe.</p> <p>Mucosal trauma should be avoided where possible</p>	Low. But recommendation is clinically sensible.
Orthodontics	<p>Safe.</p> <p>Enough time for completing physiologic bone healing process before the start of BP therapy (e.g. 4-8 weeks) should be left if possible.</p>	Low, but recommendation is clinically sensible.	<p>Likely safe.</p> <p>Some studies reported slow/ impaired tooth movements.</p> <p>No evidence to support the theory that increased turn-over can cause further accumulation of BP into the alveolar bones and trigger osteonecrosis.</p>	Low. But recommendation is clinically sensible.

## Strategie di identificazione/riduzione del rischio chirurgico – iv BP

<i>Strategy</i>	<i>Description</i>	<i>Comment</i>
Evaluation of CTX levels	Evaluation of degree of bone turnover inhibition (via CTX levels) to identify subgroups of patients at different degrees of risk.	Studies showed negative results
Discontinuation of iv BP	Discontinuation of iv BP for 1-3 months	Not supported by any evidence
Interventions within 3 months of exposure to iv BP	Surgical procedures can be safely performed during the first 3 months of therapy with iv BP.	Not supported by any. Risk during the first months is low but still present
Conservative surgical techniques	E.g. primary tissue closure	Not supported by any evidence but non-harmful and clinically sensible.
Topical antimicrobials	Chlorhexidine before, during and after surgery.	Not supported by any evidence but non-harmful and clinically sensible. It may be stopped when the wound healing process is completed.
Systemic antibiotics	(i) Antibiotic prophylaxis to be always prescribed. (ii) Antibiotic prophylaxis to be prescribed only in case of extensive surgical manipulation of the bone, and presence of concomitant factors (abscess, acute infection, other therapies etc.). A regimen of amoxicillin +/- metronidazole or clindamycin for 2 days before and 14 days after surgery has been suggested.	Not supported by any evidence. Potentially harmful due to the risk of antibiotic resistance and potential allergic reactions.
Alternative extraction techniques	Elastic-induced gradual orthodontic tooth exfoliation. An elastic (orthodontic) band is placed around the cervical part of the tooth to induce extrusive movement in 1-3 months (mean 6 weeks). Separation of the roots, endodontic therapy and regular grounding of the crown is required.	Potentially effective but data are from one case series without controls. Time-consuming and inadequate in case of acute infection.
Local anaesthetic without vasoconstrictor	Vasoconstrictor may alter the process of wound healing after surgery and may increase the risk of osteonecrosis.	Not supported by any evidence or any case report.

## 5. CONCLUSIONI & FUTURE RESEARCH

- Necessita' di RCT che valutino le diverse procedure odontoiatriche e il rischio relativo di ONJ

original article

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original article

*Annals of Oncology* 20: 137–145, 2009  
doi:10.1093/annonc/mdn526  
Published online 22 July 2008

**Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan**

C. I. Ripamonti<sup>1\*</sup>, M. Maniezzo<sup>2</sup>, T. Campa<sup>1</sup>, E. Fagnoni<sup>1</sup>, C. Brunelli<sup>1</sup>, G. Saibene<sup>3</sup>, C. Bareggi<sup>1</sup>, L. Ascani<sup>3</sup> & E. Cislighi<sup>2</sup>

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**J) after patients with acid**

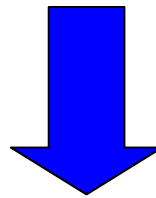
M. Roussou<sup>1</sup>,  
Λ. Bamias<sup>1</sup>

Department of Maxillofacial Surgery,

## 5. CONCLUSIONI & FUTURE RESEARCH

Attuale rivalutazione della storia naturale della ONJ: dental trigger non piu' elemento di rischio fondamentale della patogenesi

- ONJ spontanea in > 50-60% dei casi
- Estrazioni dentarie probabilmente associate a misdiagnosis di ONJ spontanea che simula patologia dentaria



Come prevedere il rischio?

Come identificare high risk individuals?

Esistono biomarkers di rischio/predisposizione?

# PHARMACO-GENETICS -GENOMICS

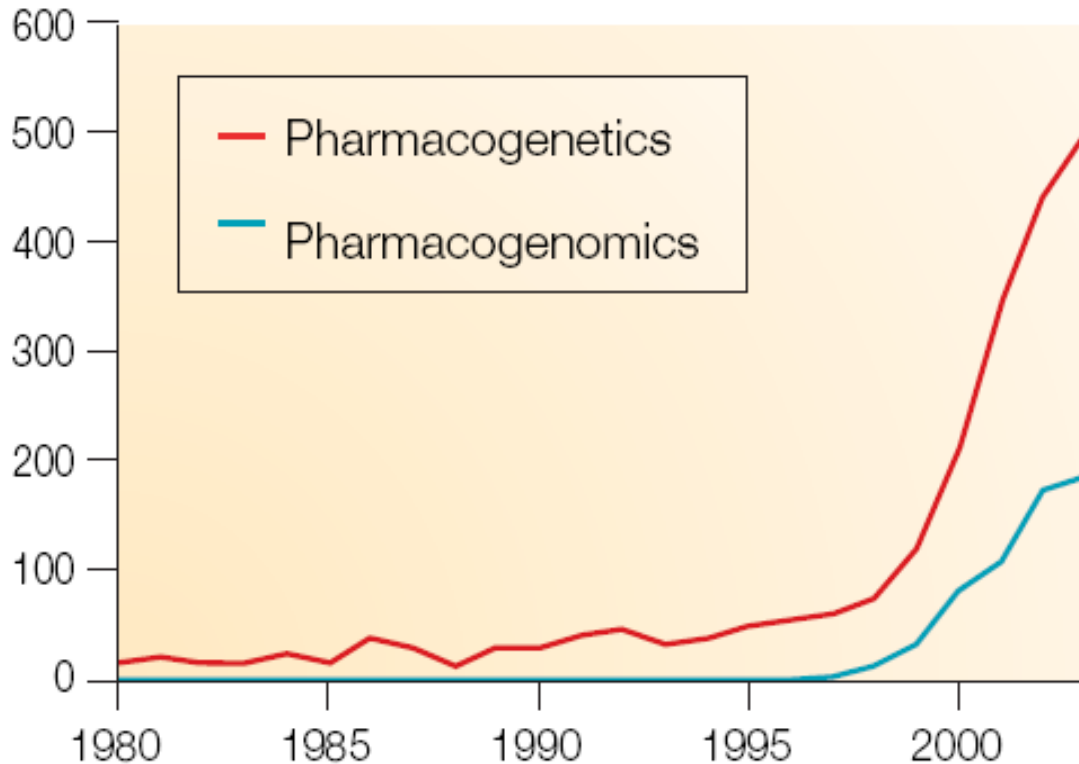
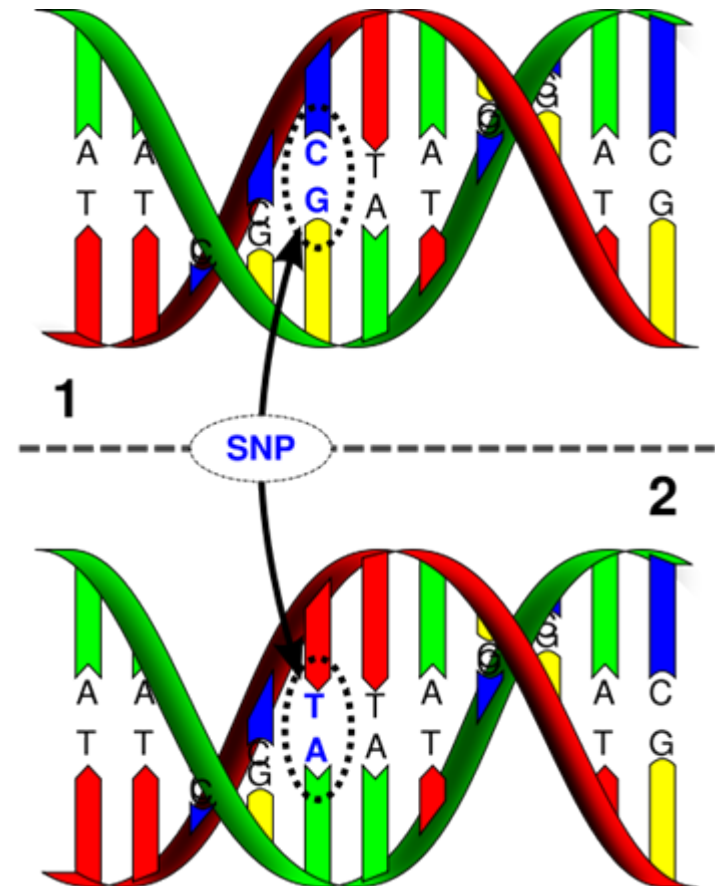


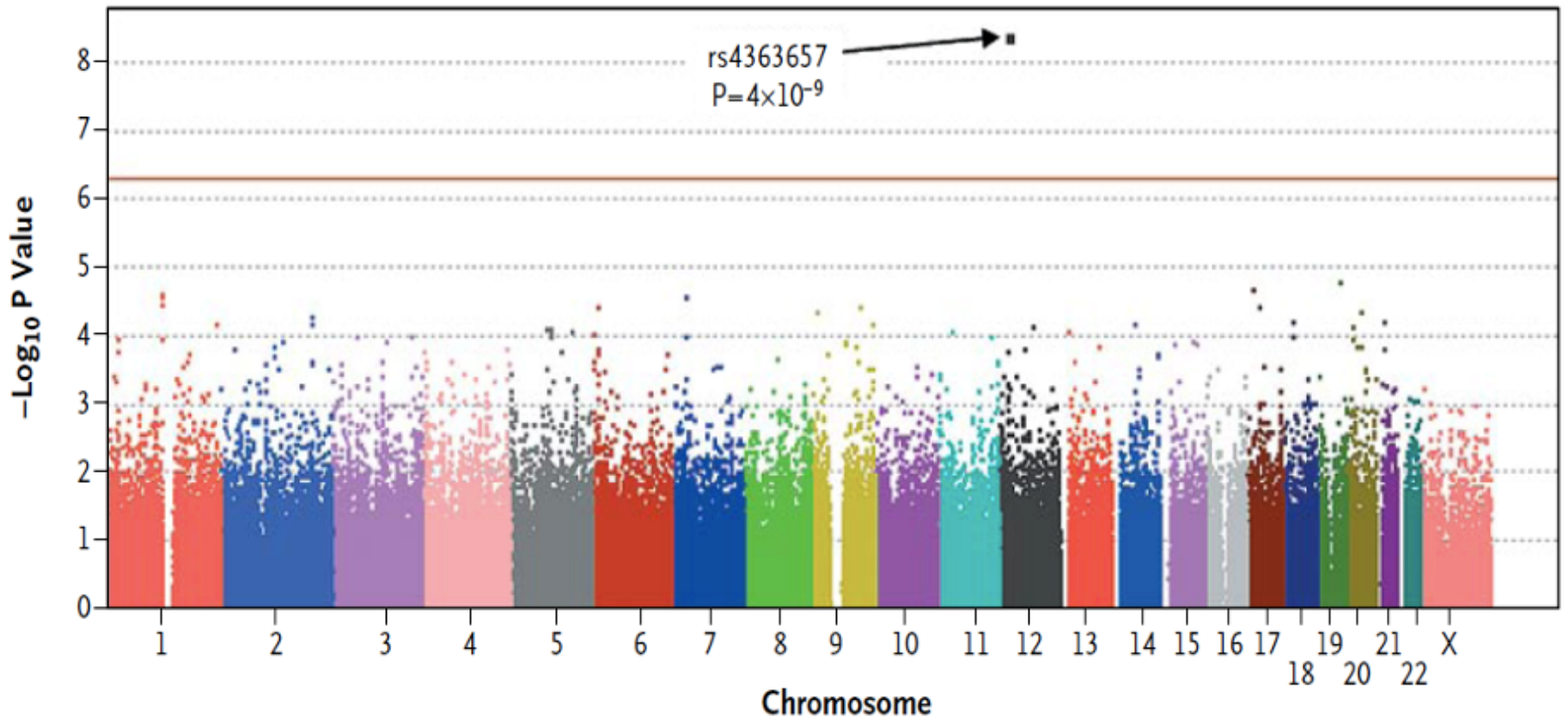
Figure 1 | **Appearance of the terms pharmacogenetics and pharmacogenomics in publications in PUBMED (National Library of Medicine).** Vogel first used the term pharmacogenetics (PGx) in 1959 (REF. 13). Publications on PGx have increased sharply in the last 5 years with the emergence of molecular genetics and genotyping technologies in clinical investigations. The term 'pharmacogenomics' first appeared in 1998.

# GENOME-WIDE ASSOCIATION STUDY (GWAS)

- Genetic Screening
- Single Nucleotide Polymorphisms (SNP)
- Candidate genes
- Genome screening



# STATIN-INDUCED MYOPATHY GWAS



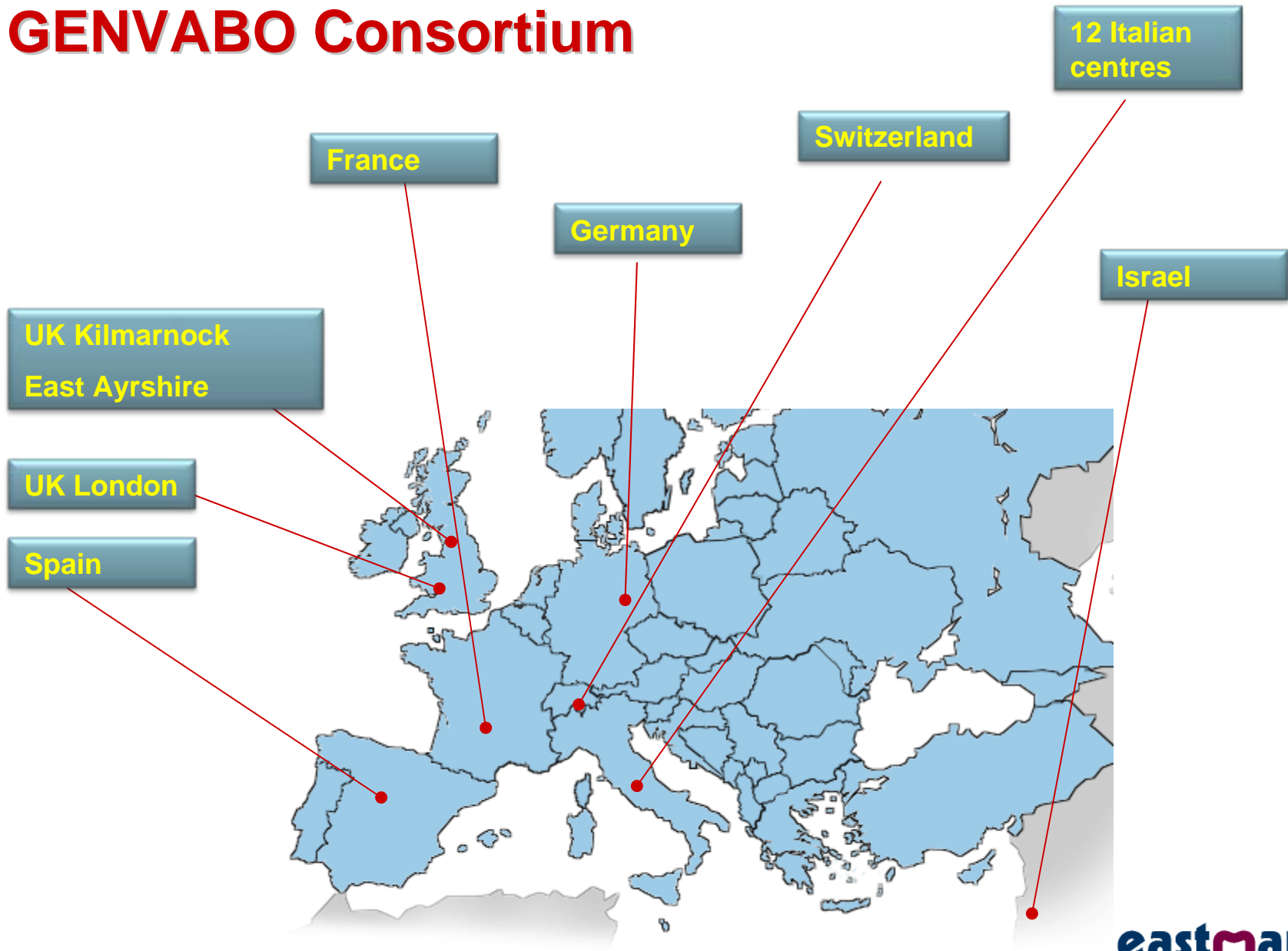
an increased risk of statin-induced myopathy. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively. (Current Controlled Trials number, ISRCTN74348595.)

# GENetic VAriants in BP-associated ONJ – GENVABO study

**Studio Europeo Multicentrico coordinato dalla University  
College London - Eastman Dental Institute**

- To ascertain potential gene variations associated with ONJ - GWAS
  - 20 collaborating clinical centres, 7 countries, 800 individuals being enrolled
  - UCL Genomics as main centre for genetic and biostatistical analysis

# GENVABO Consortium



## GENetic VAriants in BP-associated ONJ – GENVABO study

- Funding: Cancer Research UK - £0.5M (requested)
- Obiettivo: identificare uno o piu' SNP che predispongono a sviluppare ONJ quale complicanza della terapia con BF
- In fase di arruolamento. Durata prevista: 2-3 anni.
- Nuovi centri collaboranti benvenuti.

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# **OSTEONECROSI DEI MASCELLARI ASSOCIATA AI BIFOSFONATI: PREVENZIONE E VALUTAZIONE DEL RISCHIO**

## **Linee Guida, Raccomandazioni e Prospettive Future**