



Biomarkers as an aid in the management of osteoporosis

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Biomarkers as an aid in the management of osteoporosis



Agenda

- Orion Diagnostica Oy
 - Management of Postmenopausal Osteoporosis
 - Biochemical Markers of Bone Metabolism
 - Intact PINP
 - In monitoring osteoporosis therapies
 - In predicting responders in prevention and management of osteoporosis (example ; value of PINP vs BMD in oral HRT)
 - Theranostics
 - Conclusions

 - In Vitro Diagnostics Industry in Finland
-

Orion Group today



Pharmaceuticals

Orion Pharma

Clientele and focus

The best future potential lies in Orion Pharma

Wholesale and distribution of pharmaceuticals and healthcare products

Wholesale and Distribution
Oriola KD

The units share a common clientele consisting of healthcare professionals. Orion focuses on services for physicians, pharmacies, hospitals, clinics and their customers, and other healthcare professionals.

Diagnostic tests

Orion Diagnostica

Orion Diagnostica



An in-vitro diagnostic company with emphasis on point-of-care testing

Goal

- Leading position in selected areas of point-of-care (POC) testing globally

Customers

- clinical laboratories in healthcare centres and hospitals
- private practitioners
- industrial customers

Product areas focused on

- tests to detect / measure
 - Infectious diseases
 - Hormones
 - Specific proteins
 - Bone metabolism
- QuikRead® technology

Assets

Over 30 years experience of in-vitro diagnostics

Compliance with ISO 9001 Quality System since 1995

Ability to adjust core know-how to changing market needs

Over 80% of turnover from international markets

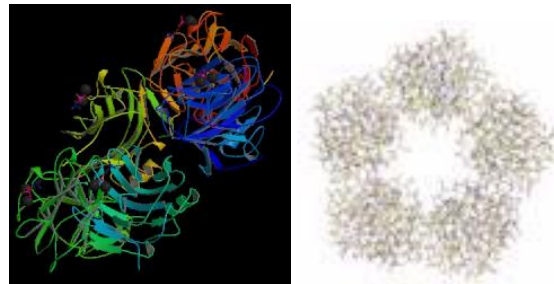
Extensive marketing network. Distributors in over 60 countries

Own marketing subsidiaries in Sweden, Norway and Denmark

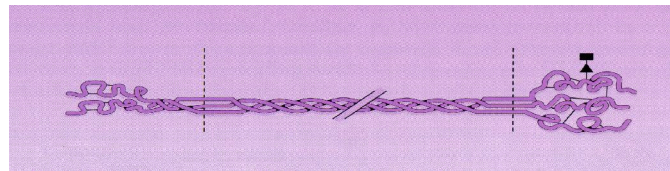
Manufacturing in Espoo and Turku

Research & Development in Espoo and Oulu (Medipolis Center)

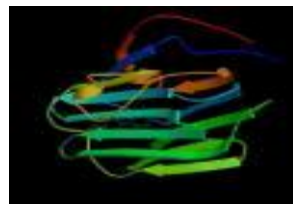
Important biomolecules to Orion Diagnostica



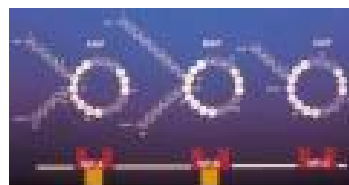
C-Reactive Protein



**Type I procollagen
(ICTP, PINP)**



**SHBG (Sex Hormone
Binding Globulin)**



Natriuretic Peptides

Osteoporosis prevention & therapy

**Osteoporosis is defined as low bone mineral density (-2,5 SD)
Appr 150 million people affected >> at risk of fractures**

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Anabolic / bone forming effect

Recombinant PTH < 0,5 bUSD
(rPTH1-34, rPTH1-84, rPTH1-31)

- Forteo/Forsteo/ E.Lilly
- PreOs*/Preatact/ NPS Pharma
- Ostabolin-C */Zelos Therap

Osteoprotegerin
recOPG /Amgen

Strontium Ranelate
Protelos /Servier Labs

* Under development
anti-RANKL / Denosumab / Amgen

Anti-catabolic / antiresorptive effect

Hormone replacement (HRT) appr. 3 bUSD
(e.g estradiol valerate Indivina /Orion)

SERMs , appr 1,5 bUS
(e.g raloxifen Evista / E-Lilly)

Bisphosphonates appr 5 bUSD
(e.g Fosamax /MSD)

Calcitonin

*Under development:
CatK inhibitors

Background information



Human skeleton

- 70 % mineralised calcium salts
 - 30 % organic matrix
 - * **90 % collagen , mainly type I collagen (27 types of collagens discovered)**
 - * **synthetised by osteoblasts and fibroblast as procollagen**
 - * **propeptide extensions released into circulation prior to assembling into collagen fibres > PICP and PINP**
 - * **in bone fibres tightly are cross-linked**
 - * **cross-links released into circulation > ICTP, NTx, CTx**
-

Metabolic Bone Markers



Bone formation

Bone alkaline phosphatase
bALP (BAP)

Osteocalcin *OC*

**Propeptides of type I
procollagen *PINP, PICP***

No POC-tests available so far

Bone resorption

Tartrate-resistant acid phosphatase
TRAP5b

Hydroxyproline

Galactosyl hydroxylysine

Bone sialoprotein

Type I collagen cross-links

Pyridinoline cross-links *Pyd, Dpd*

Cross-linked telopeptides

ICTP (CTx-MMP), *CTx, NTx*

Cathepsin K

POC-tests available for U-NTx, U-CTx

Variability of Bone Markers

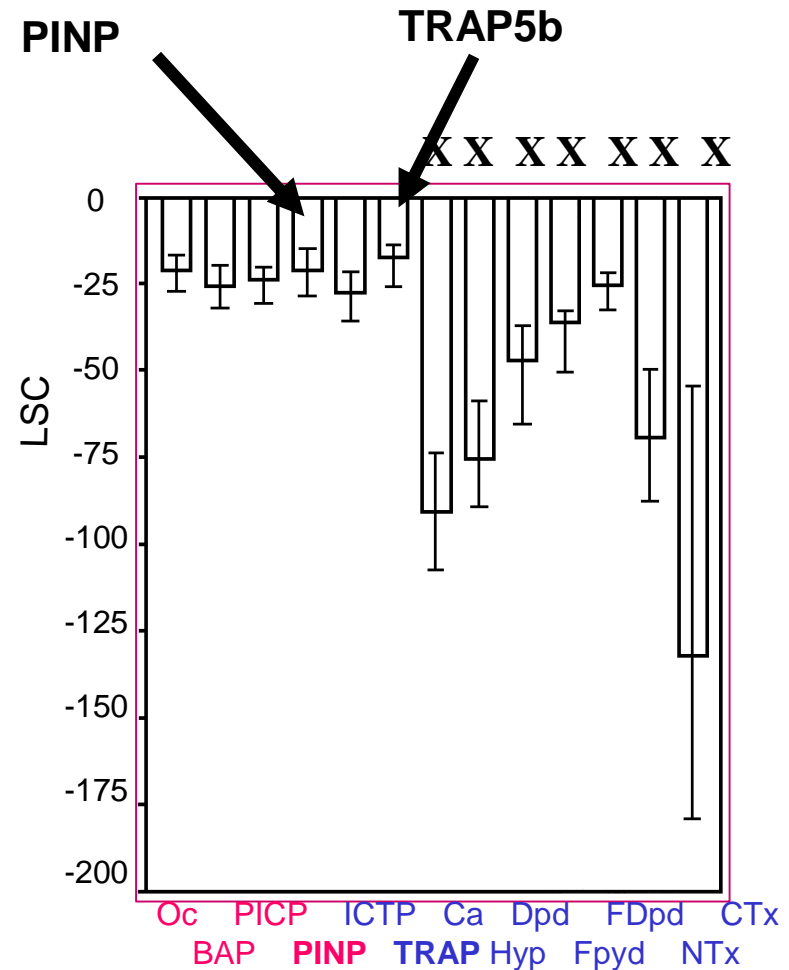


Due to the large intra-individual variability of urine markers (X), the change between two measurements has to be up to **6 times larger for urinary markers than for serum markers** to be relevant

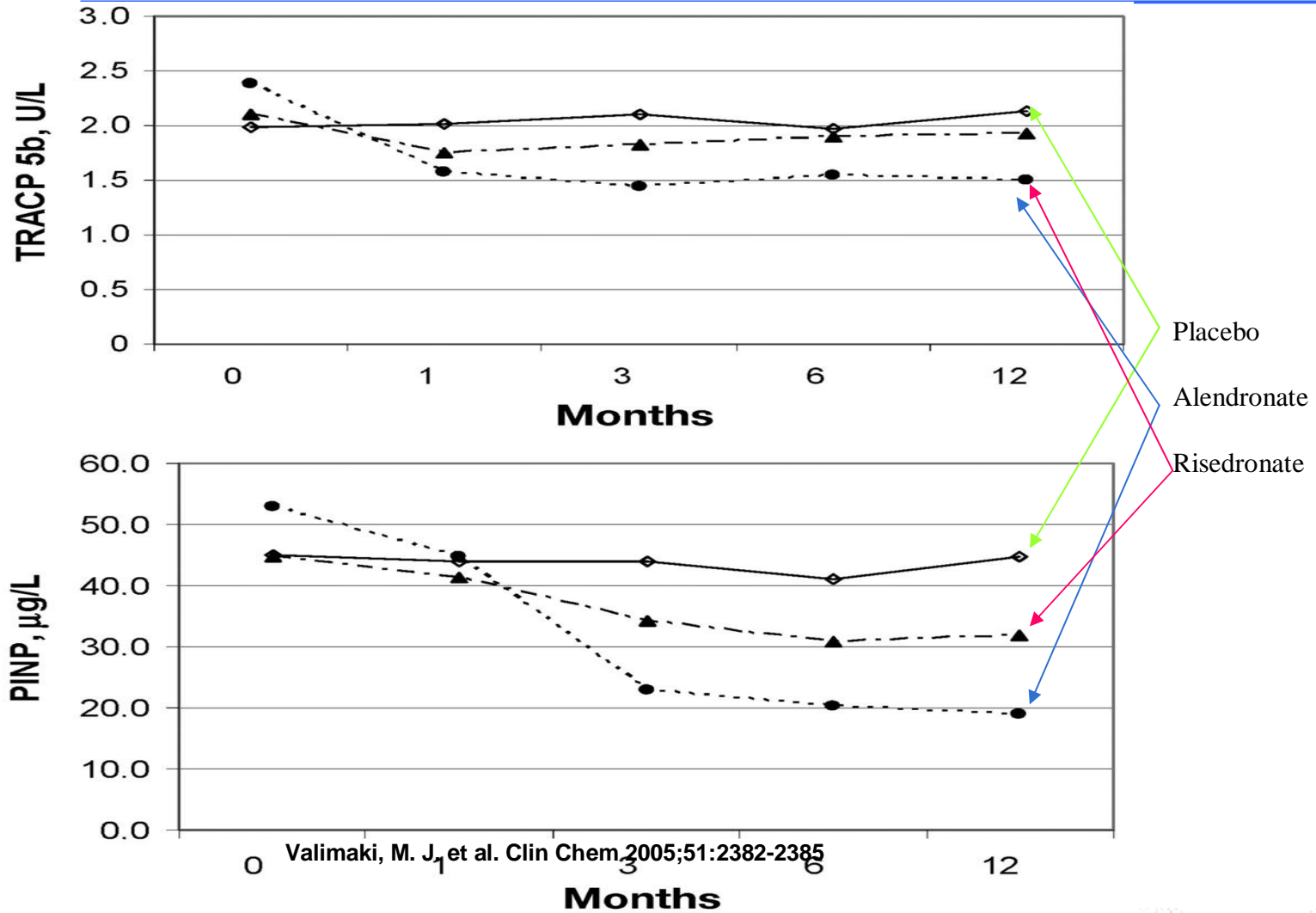
The marker showing the greatest response to treatment is not always the best!

Variability of PINP +/- 25%

(Hannon R et al, 1998)



Mean serum concentrations of TRACP5b and PINP in the study groups

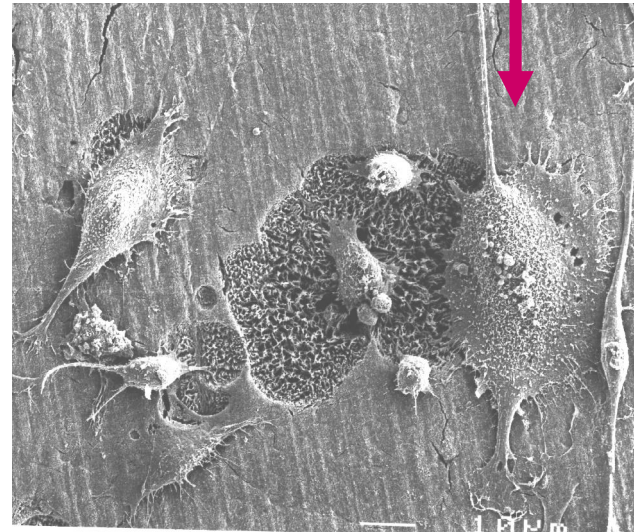


Valimaki, M. J, et al. Clin Chem, 2005;51:2382-2385

Properties of PINP

- MW 35 000
 - 2 pro α 1(I), 14250
 - 1 pro α 2(I), 5500
- phosphorylated
- partly globular, partly helical
- intact PINP and Col1 in serum
- cleared from circulation via **scavenger** receptors of the liver endothelial cells
- stable in serum for 7d at RT
- several years at -20C

Synthesised in bone by osteoblasts



Intact N-terminal Propeptide of Type I Procollagen (PINP)

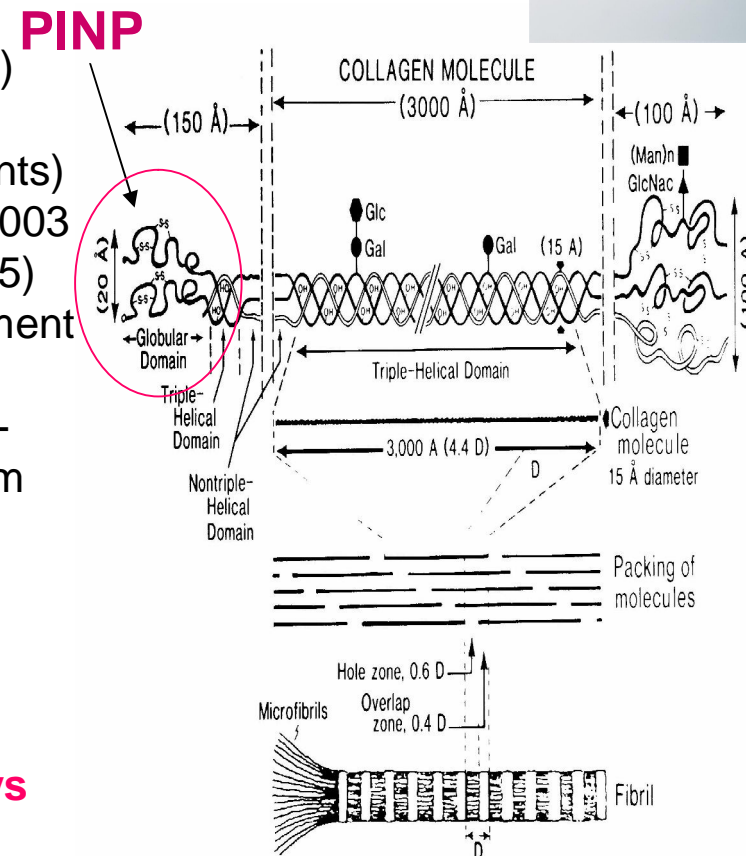


UniQ PINP RIA

- "Gold Standard" of PINP assays
- publ. in Clin.Chem. 42:6; 947-954 (1996)
- more than 200 peer-reviewed articles
- 20 patents (including 4 US, EP, JP patents)
- CE-mark , ISO 9001:2000, ISO 13485:2003
- 1st FDA approved PINP-assay (K043125)
- Intended use (510k); An aid in management of postmenopausal osteoporosis
- Assay directed to measure intact hetero- and homotrimeric forms of PINP in serum
- Due to low variability and good stability, typical Least Significant Change of 25% in monitoring therapies (incl. HRT, Bisphosphonate, SERM, recPTH)

Raw materials for next gen PINP-assays

- characterized monoclonal antibodies
- applicability to POCT and automation
- partnership & alliance opportunities



Single baseline PINP measurement as an aid in stratification postmenopausal women to hormone replacement therapy



Basal serum UniQ™ PINP > 40ug/L

Sensitivity and “specificity” of baseline PINP cut-off of 40 ug/L to predict an **increment in LS-BMD by at least 2 %** at 12 months time point in using combined continuous low dose oral Indivina (1 mg E2V + 2,5 mg MPA)

Group B	(Basal PINP>40ug/L)	n=22	
	False negative/Non-respond.	4	(<+2% change in 12 mo BMD)
	Positive/ Responders	18	(>+2% change in 12 mo BMD)
	<u>SENSITIVITY</u>		81,8%

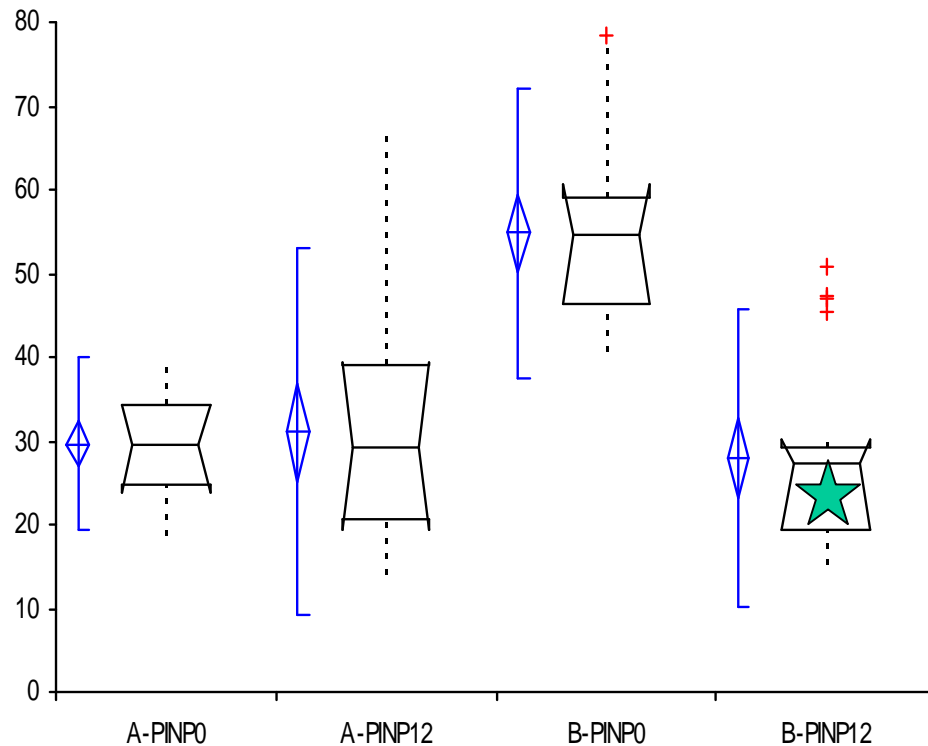
Group A	(Basal PINP<40ug/L)	n=22	
	“False” positive /Responders	4	(>+2% change in 12 mo BMD)
	Negative/Non-responders	18	(<+2% change in 12 mo BMD)
	<u>“SPECIFICITY”</u>		81,8%

Intact PINP & low-dose oral HRT

(1mgE₂V+2,5mg MPA) at baseline and after 12 months of treatment in 44 apparently healthy postmenopausal women



ug/L PINP



**Group A: Low turnover
Baseline PINP <40 ug/L**

No change in PINP or BMD

* PINP +4,7 % NS (p=0,626)

* BMD +0,7% NS (p=0,117)

**Group B: High turnover
Baseline PINP >40 ug/L**

**Highly significant change
in PINP and BMD**

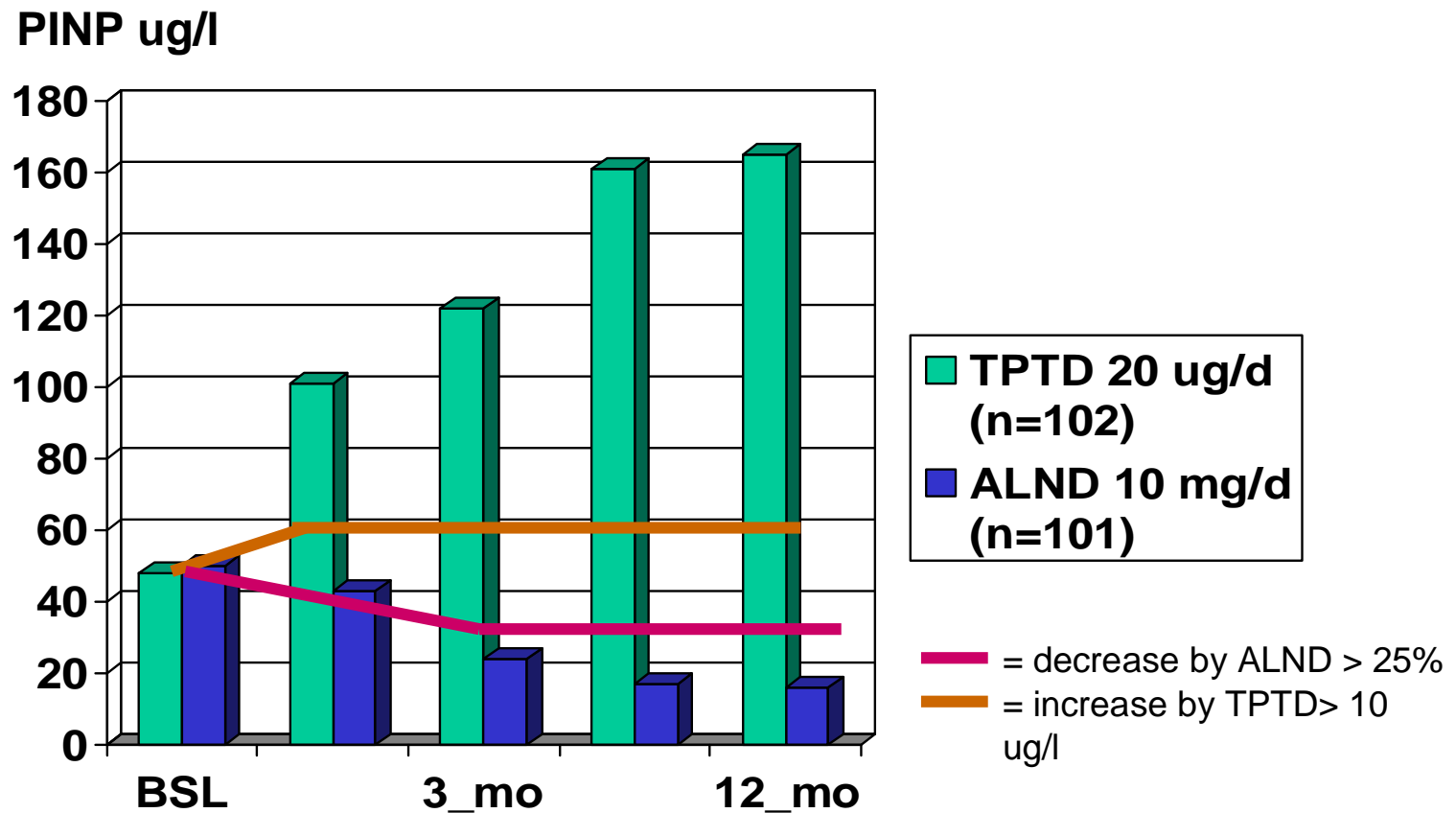
* PINP - 49,1% (p<0,0001)

* BMD +5,1% (p<0,0001)

**Group A: Low turnover
Baseline PINP <40 ug/L**

**Group B: High turnover
Baseline PINP >40 ug/L**

Serum Intact PINP reflects rate of bone turnover (Example on PINP values during anti-catabolic and anabolic osteoporosis therapies)



Source: McClung et al, 2005



The Effect of Use and Discontinuation of Long-Term Oral Low-Dose Hormone Therapy on Bone Marker (PINP) and Bone Mineral Density

Adapted from ASBMR poster #143 (2005)

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¹Orion Diagnostica Oy, Oulu, Finland, ²Deaconess Institute, Oulu, Finland,

³Orion Pharma, Espoo, Finland, ⁴University of Oulu, Oulu, Finland

Design and methods



Serum samples taken from 35 apparently healthy postmenopausal women (mean age at inclusion 55.9 years) were retrospectively analysed at the baseline (BSL) before starting HRT with a continuous combined low-dose 1mg estradiol valerate /2.5mg medroxy-progesterone acetate product (Indivina[®], Orion Pharma, Finland) and at 12-month (HRT_1y) and 108-month (HRT_9y) time points after the start of treatment and one year after discontinuation (DISC_1y).

PINP (microg/l) levels were measured using a commercially available method (UniQ[™] PINP RIA ,Orion Diagnostica Oy, Espoo, Finland). BMD was measured using DEXA (g/cm²). Statistical tests were performed using a non-parametric Mann-Whitney test and a parametric paired samples t-test of Analyse-It[™] (version 1.6.2) Statistical significance was defined as p-value < 0.05.

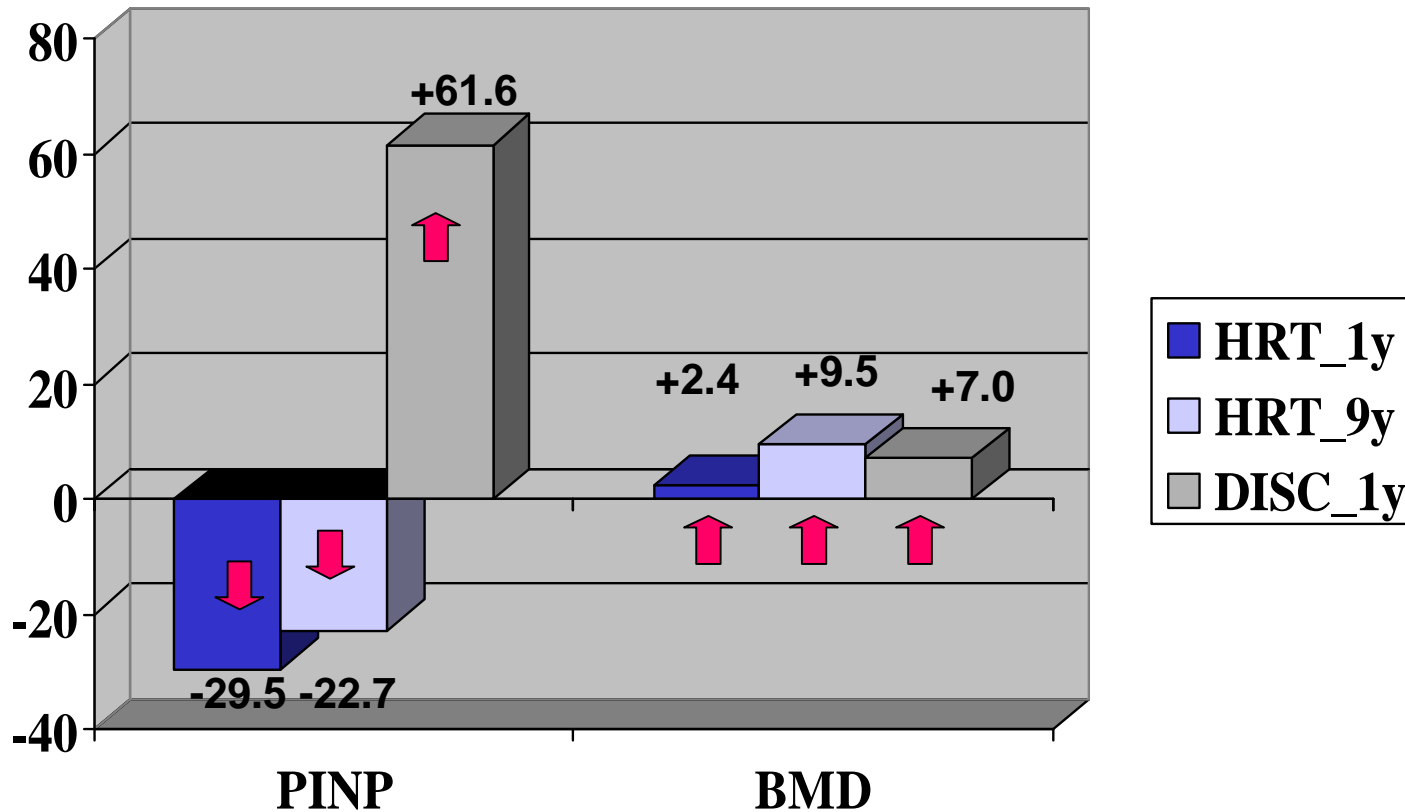
The results were first assessed as a single non-classified group (n=35). Individuals were also divided into two groups based on data published by J Heikkinen and J Haapalahti (Ref). 18 cases are classified as having low bone turnover (LOW , PINP <40 ug/l) and 17 cases as having high bone turnover (HIGH, PINP> 40 ug/l). The two groups were found to be similar in age at inclusion.

Effect of the use and discontinuation of HRT vs. the baseline

Non-classified group (n = 35)



Change (%) from the baseline level



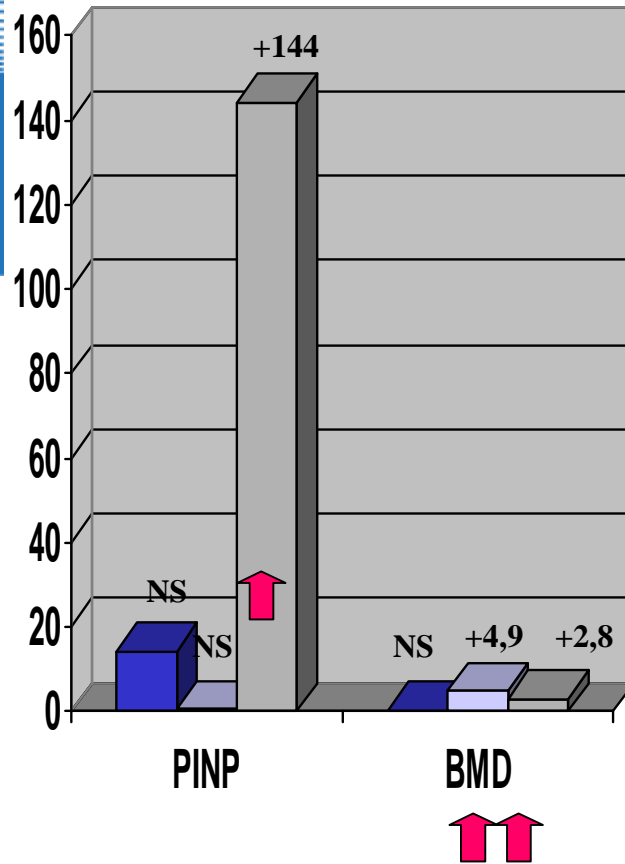
↓ = p < 0.05, decrease from HRT_9y ↑ = p < 0.05, increase from HRT_9y

Effect of the use and discontinuation of HRT vs. the baseline; Low vs High bone turnover groups

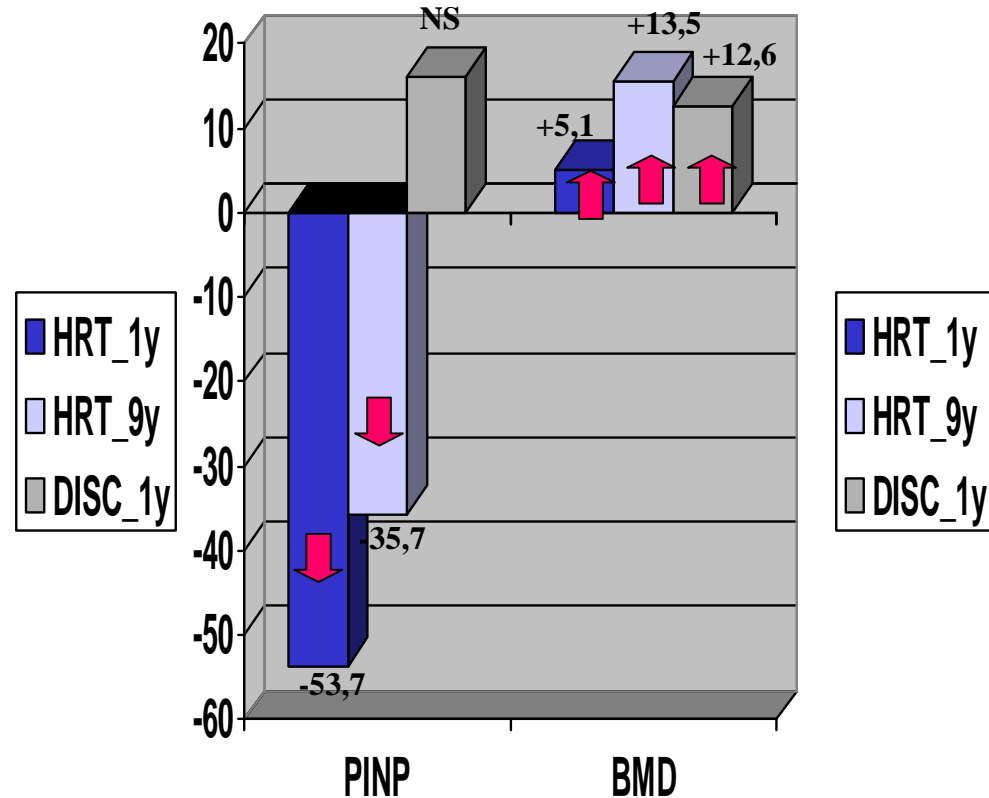


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Low turnover group, n=18



High turnover group, n= 17



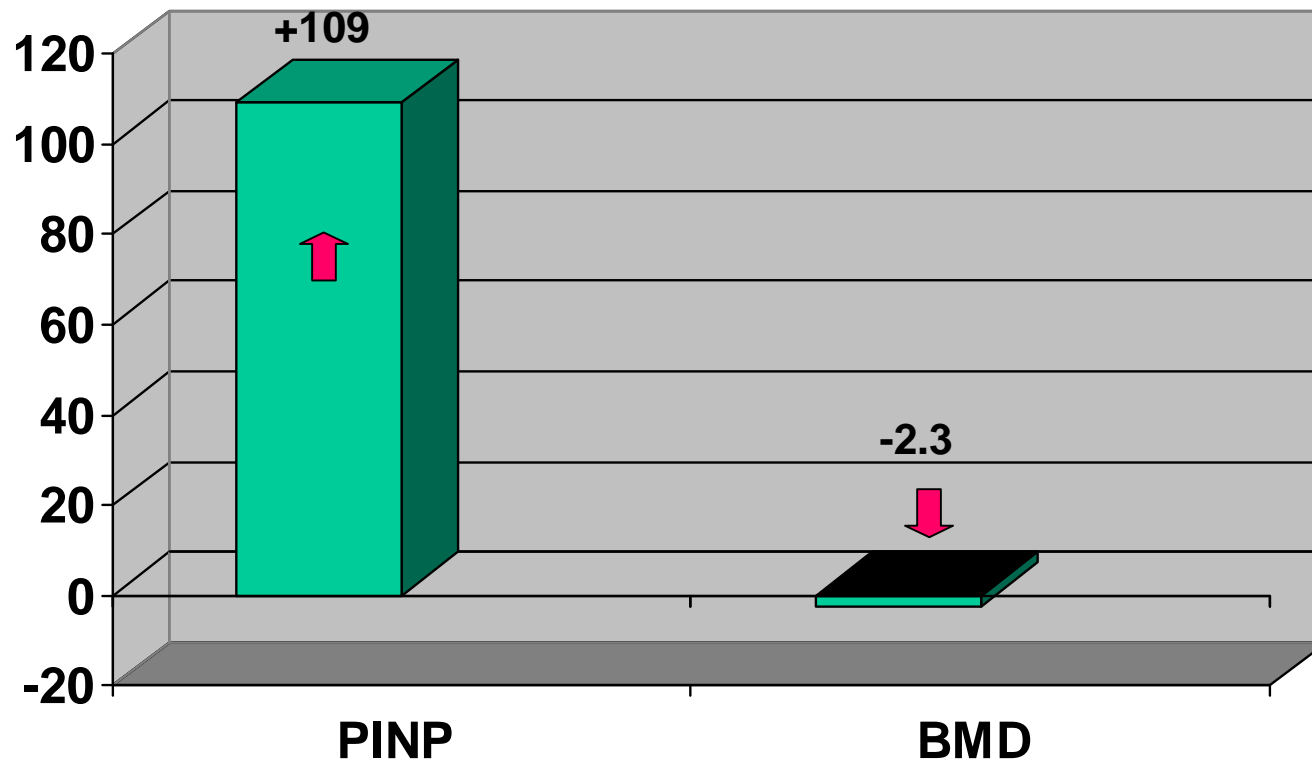
= p < 0.05, decrease from the baseline
 = p < 0.05, increase from the baseline

Effect of discontinuation of HRT vs. 9-year use of HRT

Non-classified group (n = 35)



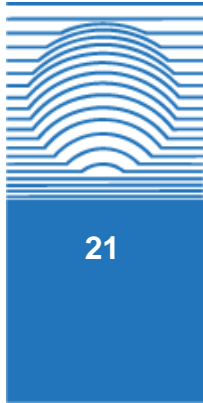
Change (%) from the HRT_9y level



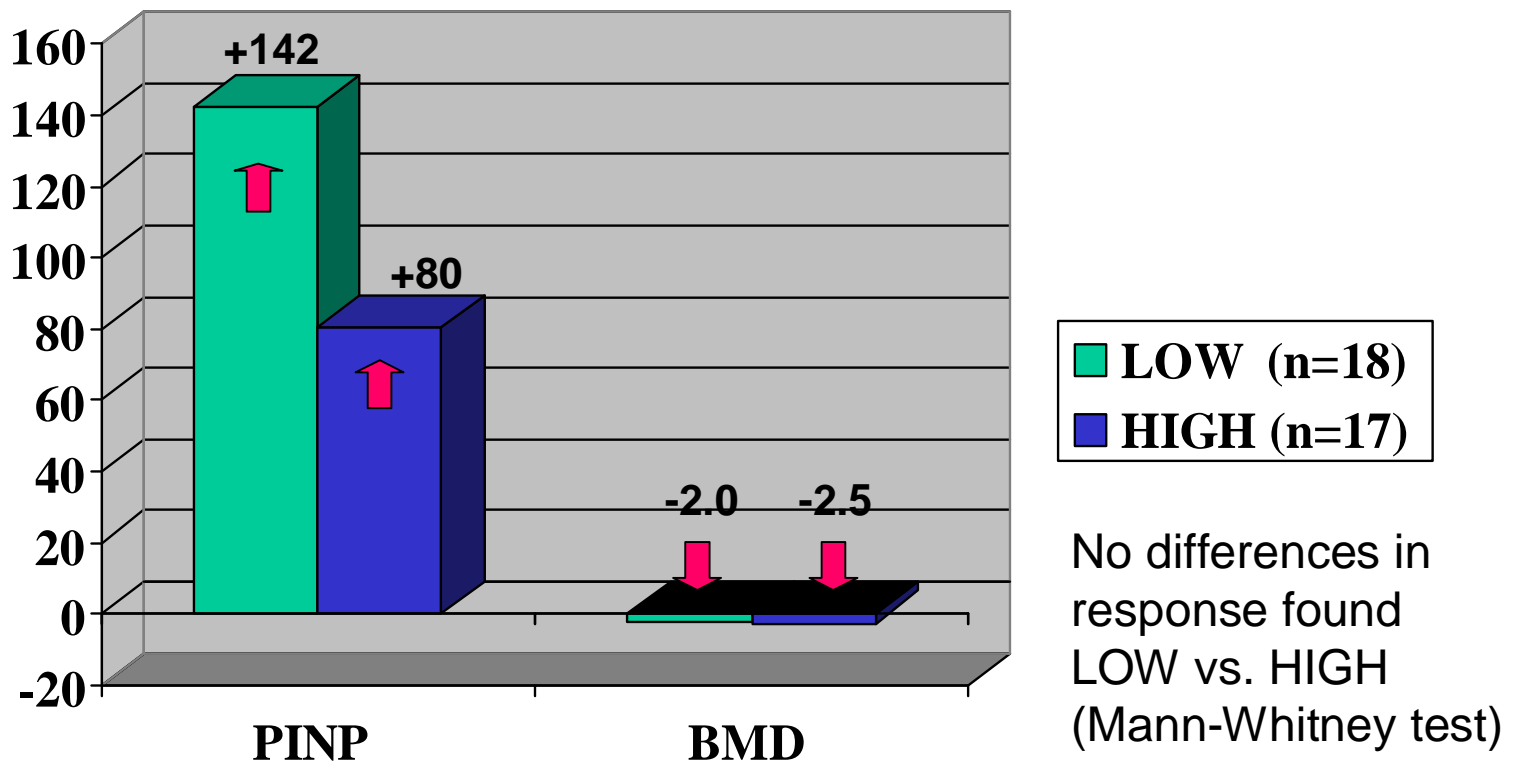
↓ = p < 0.05, decrease from HRT_9y ↑ = p < 0.05, increase from HRT_9y

Effect of discontinuation of HRT vs. 9-year use of HRT

Low and High bone turnover groups



Change (%) from the HRT_9y level



↓ = p < 0.05, decrease from HRT_9y ↑ = p < 0.05, increase from HRT_9y

Conclusions of the study



Discontinuation of long-term oral dose hormone replacement within one year leads to highly significant decrease in BMD and highly significant increase in PINP.

A biochemical marker of bone turnover, serum intact PINP, shows **theranostic potential in the prediction of skeletal response** to HRT at both initiation and discontinuation of oral HRT.

The benefits of HRT to bone, measured as a change in BMD, **can be predicted prior to therapy by a single PINP measurement**. Only those postmenopausal women with PINP > 40 microg/l (high bone turnover group) show a sharp skeletal response to even a low dose of HRT.

Theranostics = **THERA**peutics + diag**NOSTICS**
(need to optimize Rx ; only 40 -70 % drugs work as assumed)



Personalized medicine , Predictive medicine , Integrated medicine, Pharmacodiagnosics, Pharmacogenomics, Rx/Dx-partnering

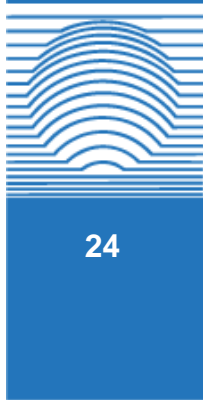
Examples; therapy vs diagnostics combinations;

- Herceptin vs Her2 protein in breast cancer
- 6-mercaptopurine & TPMT gene in childhood leukemia
- Camptosar vs UGT1A1 gene variant in colon cancer
- Drug metabolism vs cytochrome P450 enzyme genes
- Warfarin & 2C9 & vit K epoxide reductase enzymes , blood clot prevention
- Tamoxifen vs PKA gene in breast cancer
- **Response to osteoporosis therapies vs collagen turnover using Intact PINP as biomarker (outcome prediction)**

Theranostics is effective tool in guiding therapies;

- Disease risk prediction, diagnosis and prognosis
- Stratification of patients and therapies
- Monitoring therapeutic response

Summary



- Biomarkers as an aid in the management of age-related chronic diseases such as osteoporosis have shown their clinical utility
 - It can be envisaged that biomarkers with optimal features are going to increasingly guide individual preventive and therapeutic options
 - Serum based collagen derived markers of bone metabolism, such as Intact PINP, form solid basis for further development of test formats for monitoring osteoporosis therapies with good theranostic potential
 - Availability of easy-to-use bone marker tests will improve compliance and adherence to osteoporosis therapies
-
- **Orion Diagnostica`s proprietary PINP technology offers template for partnerships and alliances with academy and industries, especially with IVD and pharma-companies**
-

Finnish In Vitro Diagnostics Industry Cluster

FIVDIC members (as of Jan 2006)



25 companies , > 1700 employees,
appr 250 m€ net sales

AniBiotech Oy, **Arctic Diagnostics Oy**, **BioChange Oy**,
Biofons Oy, **BioMarket Oy**, **Biogenon Oy** , **BioTop Oy**, **FIT**
Biotech Oyj Plc, **Geneos Oy**, **GenXpress Oy**, **Headman Oy**,
HyTest Oy Ltd, **InnoTrac Diagnostics Oy**, **Jurilab Oy**,
Labmaster Oy, **Magnasense Ltd**, **Medix Biochemica Oy**,
MoBiDiag Oy, **Nanobac Oy Ltd**, **Orion Diagnostica Oy**,
PerkinElmer Life Sciences, **Raisio Life Science, Oy** **Reagena**
Ltd, **Suomen Bioanalytiikka Oy**, **Thermo Electron**
Corporation

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Operative targets of FIVDIC



To Increase Competitiveness of IVD-industry by

1. National IVD-related technology programs
 2. Targeted IVD-training for the whole personnel of FIVDIC-companies
 3. IVD-targeted Graduate School
 4. Networking and Benchmarking
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