

MicroVue™ Bone PYD EIA

An enzyme immunoassay for the quantitation pyridinium crosslinks in human urine

For *in vitro* diagnostic use.

Rx ONLY

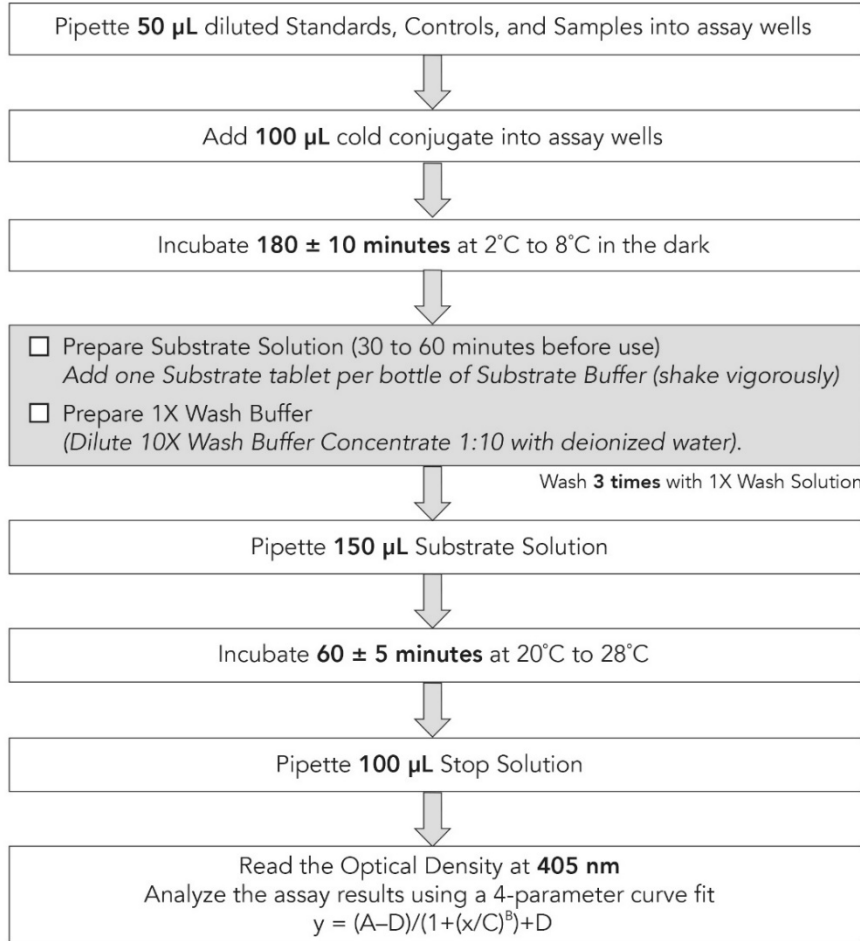
A symbols glossary can be found at quidel.com/glossary.

SUMMARY

Reagents, Standards, Controls, and Samples Preparation

- Prepare Enzyme Conjugate with Assay Buffer Solution, store at 2°C to 8°C (add 7 mL cold Assay Buffer per vial of Conjugate).
- Dilute Standards, Controls, urine specimens 1:10 with Assay Buffer Solution (50 µL sample + 450 µL Assay Buffer).

Assay Procedure





INTENDED USE

MicroVue PYD is a urinary assay that provides a quantitative measure of the excretion of pyridinium crosslinks as an indicator of type I collagen resorption, especially bone collagen.

SUMMARY AND EXPLANATION

Approximately 90% of the organic matrix of bone is type I collagen, a triple helical protein.¹ Type I collagen of bone is crosslinked by specific molecules which provide rigidity and strength. Crosslinks of mature type I collagen in bone are the pyridinium crosslinks, pyridinoline (PYD) and deoxypyridinoline (DPD).^{1,2} PYD and DPD are formed by the enzymatic action of lysyl oxidase on the amino acid lysine.³ They are released into the circulation during the bone resorption process.²⁻⁵ Pyridinium crosslinks are excreted unmetabolized in urine and are unaffected by diet,⁶ making them suitable for assessing resorption.

Bone is constantly undergoing a metabolic process called remodeling.^{2,7} This includes a degradation process, bone resorption, mediated by the action of osteoclasts, and a building process, bone formation, mediated by the action of osteoblasts.^{2,7} Remodeling is required for the maintenance and overall health of bone and is tightly coupled; that is, resorption and formation are in balance.⁷ In abnormal states of bone metabolism this process becomes uncoupled and, when resorption exceeds formation, this results in a net loss of bone.⁷ The measurement of specific degradation products of bone matrix provide analytical data of the rate of bone metabolism.^{2,4,5}

Osteoporosis is a metabolic bone disease characterized by abnormal bone remodeling. It is a systemic skeletal disease characterized by low bone mass and Microarchitectural deterioration of bone tissue, with a consequent increase in susceptibility to fractures.⁸ The most common type of osteoporosis occurs in postmenopausal women as a result of the estrogen deficiency produced by the cessation of ovarian function.⁷ Restoration of premenopausal estrogen levels by replacement therapy prevents bone loss and osteoporosis.⁷⁻⁹ Estrogens and a class of compounds known as bisphosphonates are antiresorptive therapies which can be used to prevent bone loss or treat osteoporosis.⁷⁻¹⁰ Osteoporosis can also result from attaining an inadequate peak bone mass during the growing years, an age-related imbalance of bone remodeling with a net excess of resorption, and a number of clinical conditions and therapies which induce bone loss or bone remodeling imbalances.⁷ These include endocrine diseases such as hypogonadism, hyperthyroidism, hyperparathyroidism, and hypercortisolism; gastrointestinal diseases related to nutrition and mineral metabolism; connective tissue diseases; multiple myeloma; chronic immobilization, alcoholism, or tobacco use; and chronic therapy with heparin or corticosteroids.⁷ Other diseases characterized by abnormal bone remodeling include Paget's disease and cancers metastatic to bone.³

For the MicroVue PYD assay, technology was employed to produce a monoclonal antibody that demonstrates specificity for pyridinium crosslinks.¹¹ The specificity of the monoclonal antibody used in the MicroVue PYD EIA allows for simple, convenient, reproducible and direct quantitation of PYD and DPD in urine.

PRINCIPLE OF THE PROCEDURE

The MicroVue PYD EIA is a competitive enzyme immunoassay in a Microtiter strip format utilizing a monoclonal anti-pyridinium crosslinks antibody to measure PYD and DPD in urine. The PYD and DPD in the sample compete for the antibody with PYD coated on the strip. The reaction is detected with a pNPP substrate. MicroVue PYD results are corrected for urinary concentration by creatinine.

REAGENTS AND MATERIALS PROVIDED

96 Assays for Pyridinium Crosslinks

MicroVue PYD EIA kit contains the following:

A Pyridinoline Standards	Parts 4251-4256	0.3 mL, 1 each
B PYD purified from human urine in 10 mmol/L phosphoric acid containing sodium azide (0.05%) as a preservative		
C		
D		
E		
F		
L Low/High Controls	Parts 4257, 4258	0.3 mL, 1 each
H PYD Purified from human urine in 10 mmol/L phosphoric acid containing sodium azide (0.05%) as a preservative		
1 Coated Strips	Part 4668	12 each
PYD purified from bovine bone absorbed onto stripwells		
2 Stop Solution	Part 4702	15 mL
0.5N NaOH		
3 10X Wash Buffer	Part 4703	55 mL
Nonionic detergent in a buffered solution containing sodium azide (0.05%) as a preservative		
4 Assay Buffer	Part 4704	55 mL
Nonionic detergent in a buffered solution containing sodium azide (0.05%) as a preservative		
5 Substrate Buffer	Part 4705	3 x 10 mL
A diethanolamine and magnesium chloride solution containing sodium azide (0.05%) as a preservative		
6 Substrate Tablets	Part 0012	3 x 20 mg
p-Nitrophenyl phosphate		
7 Enzyme Conjugate	Part 4250	3 each
Lyophilized murine monoclonal anti-pyridinium crosslinks antibody conjugated to alkaline phosphatase containing buffer salts and stabilizers		
Plate Tape Cover	Part 0047	3 each

MATERIALS REQUIRED BUT NOT PROVIDED

- Micropipettes to deliver 50 μ L to 300 μ L
- Items suitable for liquid measurement of 7 mL to 300 mL
- Container for wash buffer dilution
- Tubes for dilution of samples, standards and controls
- Deionized or distilled water
- Plate reader capable of reading at 405 nm
- 4-parameter calibration curve fitting software
- Creatinine values (mmol/L) for urine samples

WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Treat specimen samples as potentially biohazardous material. Follow Universal Precautions when handling contents of this kit and any patient samples.
- Use the supplied reagents as an integral unit prior to the expiration date indicated on the package label.

- Store assay reagents as indicated.
- Do not use Coated Strips if pouch is punctured.
- Test each sample in duplicate.
- 0.5N NaOH is considered corrosive and can cause irritation. Do not ingest. Avoid contact with skin, eyes or clothing. If contact is made, wash with water. If ingested, call a physician.
- Sodium azide is used as a preservative. Incidental contact with or ingestion of buffers containing sodium azide may cause irritation to the skin, eyes, or mouth. Only use buffers for intended purposes and avoid contact with acids. Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. Upon disposal, flush with a large volume of water to prevent azide build-up.
- The substrate buffer contains diethanolamine and may cause irritation to the eyes and/or skin with prolonged contact. Contacted areas should be immediately washed with soap and water.
- Standards and Controls are in 10 mmol/L phosphoric acid. Avoid contact with skin, eyes or clothing. Do not ingest. If contact is made, wash with water. If ingested, call a physician.
- Use of multichannel pipets or repeat pipettors is recommended to ensure timely delivery of reagents.
- For accurate measurement of samples, add samples and standards precisely. Pipet carefully using only calibrated equipment.
- Do not use a Microassay well for more than one test.
- Using incubation times and temperatures other than those indicated in the *ASSAY PROCEDURE* section may give erroneous results.
- The MicroVue PYD Standards, Controls, Coated Strips, and urine samples are light sensitive. Avoid prolonged exposure to light, especially direct or indirect sunlight. Store reagents in the dark when not in use. Samples and reagents are not significantly affected by normal, artificial laboratory lighting when handled as directed in the *ASSAY PROCEDURE*.
- Do not allow Microassay wells to dry once the assay has begun.
- When [adding or] removing liquid from the Microassay wells, do not scrape or touch the bottom of the wells.
- A wash bottle or automated filling device should be used to wash the plate (*ASSAY PROCEDURE*, Step 8). For best results, do not use a multichannel pipette to wash the Microassay plate.
- This assay has been validated for manual washing.
- Testing should be performed in an area with adequate ventilation.
- Dispose of containers and unused contents in accordance with Federal, State and Local regulatory requirements.
- Wear suitable protective clothing, gloves, and eye/face protection when handling the contents of this kit.
- Wash hands thoroughly after handling.
- For additional information on hazard symbols, safety, handling and disposal of the components within this kit, please refer to the Safety Data Sheet (SDS) located at quidel.com.

REAGENT PREPARATION

Wash Buffer – See Procedural Note in *ASSAY PROCEDURE* section

Prepare required amount of 1X Wash Buffer (see table in *ASSAY PROCEDURE* section) by diluting 10X Wash Buffer concentrate 1:10 with deionized water. Store at 20°C to 28°C. Use 1X Wash Buffer within 21 days of preparation.

Special Washing Instructions: Prepare 1X Wash Buffer as above and store at 2°C to 8°C until use.

Enzyme Conjugate

Prepare Enzyme Conjugate within 2 hours of use. Reconstitute each required vial of Enzyme Conjugate (see table) with 7 mL cold Assay Buffer. Store reconstituted Enzyme Conjugate at 2°C to 8°C until use.

Working Substrate Solution

Bring the Substrate Buffer to 20°C to 28°C before beginning the assay. (Two hours to overnight recommended.) Prepare Working Substrate Solution within 1 hour of use. Put one Substrate Tablet into each required bottle of 20°C to 28°C Substrate Buffer (see table). Allow 30 to 60 minutes for tablet(s) to dissolve. Vigorously shake bottle(s) to completely mix.

STORAGE

Store kit at 2°C to 8°C.

Store unused reagents at 2°C to 8°C.

Store 1X Wash Buffer (10X diluted) at 20°C to 28°C.

SPECIMEN COLLECTION AND STORAGE

The MicroVue PYD EIA can be carried out using preservative free First Morning Void (FMV) or Second Morning Void (SMV) urine collections. Longitudinal collections (e.g. when assessing changes in resorption) should be collected at approximately the same time each day. Keep the urine sample refrigerated (2°C to 8°C) for storage of less than 7 days, or freeze the sample at $\leq -20^{\circ}\text{C}$ for longer storage. Do not subject sample to more than 3 freeze/thaw cycles. Avoid prolonged exposure to light, especially sunlight. During routine processing, samples are not affected by normal, artificial laboratory lighting.

ASSAY PROCEDURE

Read entire Product Insert before beginning the assay.

See *REAGENT PREPARATION* before proceeding.

PROCEDURAL NOTE: The MicroVue PYD EIA is sensitive to washing conditions. The **entire wash step** should be completed **within 2 minutes**. **If the wash step CANNOT be completed within 2 minutes, follow the *Special Washing Instructions located in the REAGENT PREPARATION and Washing Step sections.***

Determine amount of each reagent required for the number of strips to be used.

# of Strips	4	6	8	12
# of Samples (tested in duplicate)	8	16	24	40
Enzyme Conjugate (vial)	1	1	2*	2*
Substrate (bottle)	1	1	2*	2*
1x Wash Bottle (mL)	100	150	200	300

*When more than one bottle or vial is to be used, combine the contents and mix prior to use.

Sample/Enzyme Conjugate Incubation

1. Dilute samples, Standards and Controls 1:10 with Assay Buffer (e.g. 50 μL sample + 450 μL Assay Buffer).
2. Remove Stripwell Frame and the required number of Coated Strips from the pouch (see table). Ensure that the pouch containing any unused strips is completely resealed.
3. Place desired number of Coated Strips in the Stripwell Frame. Label strips to prevent mix-up in case of accidental removal from Stripwell Frame.
4. Add 50 μL diluted Standard, Control or sample to each well of the Coated Strips. This step should be completed within 30 minutes.
5. Prepare Enzyme Conjugate within 2 hours of use. Reconstitute each required vial of Enzyme Conjugate (see table) with 7 mL cold (2°C to 8°C) Assay Buffer. Store reconstituted Enzyme Conjugate at 2°C to 8°C until use.
6. Add 100 μL of reconstituted Enzyme Conjugate to each well. Cover strips with Tape Cover provided. Incubate for 3 hours (± 10 minutes) at 2°C to 8°C. This incubation should be carried out in the dark.

7. Prepare Working Substrate Solution within 1 hour of use. Put one Substrate Tablet into each required bottle of 20°C to 28°C Substrate Buffer (see table). Allow 30 to 60 minutes for tablet(s) to dissolve. Vigorously shake bottle(s) to completely mix.

Washing Step

8. Prepare required amount of 1X Wash Buffer (see table) by diluting 10X Wash Buffer 1:10 with deionized water. Manually invert/empty strips (from step 6). Add at least 250 µL of 1X Wash Buffer to each well and manually invert/empty strips. Repeat two more times for a total of three washes. Vigorously blot the strips dry on paper towels after the last wash. While strips are inverted, carefully wipe bottom of strips with a lint-free paper towel to ensure that the bottom of the strips are clean.

Special Washing Instructions: Perform wash step as above, using cold (2°C to 8°C) 1X Wash Buffer. After last wash, allow strips to drain for 5 to 10 minutes on paper towels before adding substrate.

Substrate Incubation

9. Add 150 µL of Working Substrate Solution to each well.
10. Incubate for 60 minutes (± 5 minutes) at 20°C to 28°C.
NOTE: If room temperature cannot be maintained between 20°C to 28°C and an absorbance of > 2.0 is not compatible with your plate reader, monitor the development of substrate in the Standard A wells; stop the reaction when the optical density reaches 1.2 to 1.5; then read the strips.

Stop/Read

11. Add 100 µL of Stop Solution to each well. Add Stop Solution in the same pattern and time intervals as the Substrate Solution addition.
12. Read the optical density at 405 nm. Assure that no large bubbles are present in the wells and that the bottom of the strips are clean. Strips should be read within **15 minutes** of Stop Solution addition.
13. Use quantitation software with a 4-parameter calibration curve fitting equation to analyze the MicroVue PYD EIA results.

$$\text{Equation: } y = (A-D)/(1 + (x/C)^B) + D$$

14. Determine concentration of samples and Controls from the Standard curve.
 - a. Dilute samples that result in values which are greater than the highest standard control in Assay Buffer and retest. Include the dilution factor in the final calculation.
 - b. Control values should be within the range specified in the Certificate of Analysis supplied with the kit.

QUALITY CONTROL

The Certificate of Analysis included in this kit is lot specific and is to be used to verify that the results obtained by your laboratory are similar to those obtained at Quidel. The optical density values are provided and are to be used as a guideline only. The results obtained by your laboratory may differ.

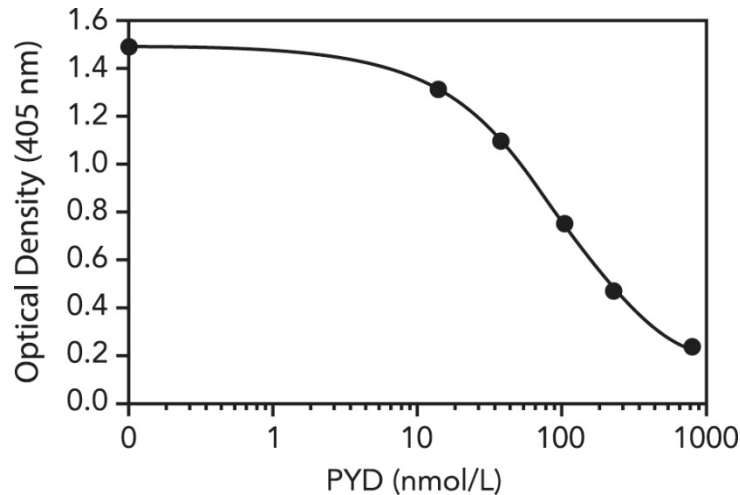
Quality control ranges are provided. The control values are intended to verify the validity of the curve and sample results. Each laboratory should establish its own parameters for acceptable assay limits. If the control values are NOT within your laboratory's acceptance limits, the assay results should be considered questionable and the samples should be repeated.

If the optical density of the MicroVue PYD Standard A is less than 0.8, the results should be considered questionable and the samples should be repeated.

INTERPRETATION OF RESULTS

Results obtained from the MicroVue PYD EIA must be corrected for variations in urine concentration by dividing the pyridinium crosslinks value (nmol/L) by the creatinine value (mmol/L) of each sample (Creatinine mg/dL x 0.088 = mmol/L). The final MicroVue PYD results will be expressed as nmol PYD & DPD/mmol creatinine.

Representative Standard Curve



LIMITATIONS OF THE PROCEDURE

While MicroVue PYD is used as an indicator of type I collagen resorption, especially bone collagen, use of this test has not been established to predict development of osteoporosis or future fracture risk. Use of this test has not been established in menopause, Paget's disease of bone, primary hyperparathyroidism or hyperthyroidism. Results may be confounded in patients afflicted with clinical conditions known to affect bone collagen resorption, e.g. bone metastases, in addition to diseases and conditions listed above. MicroVue PYD results should be interpreted in conjunction with clinical findings and other diagnostic results.

SAMPLE VALUES

MicroVue PYD reference ranges have been established for healthy males (n = 118) and healthy premenopausal females (n = 301) over 25 years of age. For the purposes of establishing reference ranges, normal subjects were defined as:

- Basically healthy, no bone, endocrine or chronic disorders
- Regular menstrual cycles (females)
- Not pregnant or breast feeding (females)
- Not currently taking any medication known to influence bone metabolism (e.g. corticosteroids, GnRH analogs, anticonvulsants, heparin, thyroid medication)

Values may be influenced by such factors as low estrogen production, low calcium intake, low physical activity or diseases known to affect bone metabolism, such as osteoporosis, Paget's disease, hyperparathyroidism, hyperthyroidism and bone metastases. Estrogen deficiency in postmenopausal women can result in elevated bone resorption. It is suggested that the premenopausal reference range be used to interpret results in postmenopausal women. Each laboratory should establish its own normal reference range. The ranges are expressed as nonparametric reference intervals (90% CI).

Sex	Range (nmol/mmol)	Mean (nmol/mmol)	SD (nmol/mmol)
Females	16.0-37.0	25.5	7.5
Males	12.8-25.6	18.5	4.4

The expected within-subject variability was determined from urine specimens from 49 healthy subjects (26 premenopausal females and 23 males) collected for five nonconsecutive days over two weeks. The average of the individual within-subject longitudinal variation was 15%. Between-subject variability is reflected in the nonparametric reference intervals shown above.

PERFORMANCE CHARACTERISTICS

Antibody Specificity

The monoclonal anti-pyridinium crosslinks antibody has selective, high affinity for free PYD and DPD and negligible binding to PYD and DPD peptides.

	% Reactivity
Free PYD	100%
Free DPD	100%
PYD/DPD peptides \geq 1000 MW	< 2.5%

Sensitivity

The minimum detection limit of the MicroVue Bone PYD EIA is 7.5 nmol/L, determined by the upper 3 SD limit in a zero standard study.

Recovery – Spike Recovery

Spike recovery was determined by adding a known quantity of purified PYD to urine samples with different levels of endogenous PYD. Typical results are provided below.

Sample	Endogenous (nmol/L)	Added (nmol/L)	Observed (nmol/L)	Recovery %
1	16.7	68.2	84.1	99
2	71.0	68.2	140.8	102
3	141.0	68.2	215.5	109

Recovery – Linearity

Linearity was determined by serially diluting samples and comparing observed values with expected values. Typical results are provided below.

Sample	Dilution Factor	Observed (nmol/L)	Expected (nmol/L)	Recovery %
1	neat	261.6	–	–
	1:2	127.8	130.8	98
	1:4	59.9	65.4	92
	1:8	31.1	32.7	95
2	neat	382	–	–
	1:2	183.2	191.0	96

Sample	Dilution Factor	Observed (nmol/L)	Expected (nmol/L)	Recovery %
	1:4	90.4	95.5	95
	1:8	57.9	57.1	95
3	neat	412.3	–	–
	1:2	199.0	206.2	96
	1:4	98.2	103.1	95
	1:8	47.8	54.5	98

Precision

Within-run precision was determined for 52 replicates of 3 samples on 1 plate from each of 3 kit lots (3 plates total). Between run precision was determined for 3 samples run in 8 separate plates from each of 3 kit lots (24 plates total). Samples shown below represent a range of nmol/L values. For a female with a creatinine of 5.0 mmol/L, samples 1 through 3 represent low normal, high normal, and elevated resorption (13.2 nmol/mmol, 32.0 nmol/mmol, and 81.4 nmol/mmol, respectively).

PYD (nmol/L)	Within-run ¹ C.V. (%)	Between-run ² C.V. (%)
66	9.9	11.2
160	7.0	5.8
407	6.6	3.9

¹n = 52 ²n = 8 runs

CLINICAL STUDIES

Clinical studies were performed to evaluate urine pyridinium crosslink levels obtained using the MicroVue PYD EIA. The first study was conducted at clinical investigation sites using 52 samples from healthy volunteers and 138 samples from patients with known bone disorders (osteoporosis, drug-induced osteoporosis, Paget's disease, hyperparathyroidism and hyperthyroidism). These diseases often involve elevated bone collagen resorption at the time of sample collection.

In the study, the MicroVue PYD EIA was compared to a research high performance liquid chromatography (HPLC) method for measuring PYD.¹² The HPLC threshold was determined, in a study of 84 healthy adult subjects, to be 50 nmol/mmol for males and 60nmol/mmol for females (95% confidence interval upper limit for each gender). One hundred and one of the 138 patients diagnosed with a bone disorder did not have elevated PYD values as measured by the HPLC. The PYD pyridinium crosslink values in healthy subjects ranged from 13.7 to 49.4 nmol/mmol and in patients ranged from 9.8 to 135.9 nmol/mmol.

Using elevated PYD determined by HPLC as the classification method, the receiver operating characteristic (ROC) technique was used to define an optimal relative sensitivity and specificity in the described population. Relative sensitivity and specificity are presented in Table 1. A two-by-two contingency table showing the number of subjects in each classification is shown in Figure 1.

Table 1

MicroVue PYD	
Relative Sensitivity	84%
Specificity	82%

Figure 1

		HPLC PYD	
		Elevated +	Elevated -
MicroVue PYD	+	38	26
	-	7	119

In a second study, the MicroVue PYD EIA results were compared in a mixed population of 39 samples from healthy subjects and 99 samples from Paget's disease patients. Although Paget's disease represents a model for identifying active bone collagen resorption, some of the patients in this study were undergoing treatment or may have been in remission, and may not have had elevated resorption at the time of sample collection. In this study, healthy subjects ranged from 12.8 to 33.2 nmol/mmol. Paget's disease patients ranged from 14.4 to 667.6 nmol/mmol.

Using the diagnosis of Paget's disease as the classification method, the ROC technique was used to define an optimal relative sensitivity and specificity in this population. Relative sensitivity and specificity are shown in Table 2. A two-by-two contingency table is shown in Figure 2.

Table 2

MicroVue PYD	
Relative Sensitivity	89%
Specificity	95%

Figure 2

		Paget's Diagnosis	
		Yes +	No -
MicroVue PYD	+	88	2
	-	11	37

ASSISTANCE

To place an order or for technical support, please contact a Quidel Representative at 800.874.1517 (in the U.S.) or 858.552.1100 (outside the U.S.), Monday through Friday, from 8:00 a.m. to 5:00 p.m., Eastern Time. Orders may also be placed by fax at 740.592.9820. For e-mail support contact custserv@quidel.com or technicalsupport@quidel.com.

For services outside the U.S.A., please contact your local distributor. Additional information about Quidel, our products, and our distributors can be found on our website quidel.com.

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REF 8010 – MicroVue PYD EIA Kit

IVD



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PI8010003EN00 (11/19)

GLOSSARY

REF

Catalogue number



CE mark of conformity

EC REP

Authorized Representative
in the European Community

LOT

Batch code



Use by



Manufacturer



Temperature limitation



Intended use

Rx ONLY

Prescription use only



Consult e-labeling
instructions for use

IVD

For *In Vitro* diagnostic use



Contains sufficient for 96 determinations

CONT

Contents/Contains

CONTROL

Control
