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Research Article

Urine Protein/Creatinine Ratio and Urine Protein Excretion: A Survey of Reference Ranges and Test Naming in Laboratory Directories

Running title: Survey of Urine Protein Test Information

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ABSTRACT

The urine protein/creatinine ratio (UP/C) and 24-hour urine protein excretion (24hUPE), are tests of renal disease and preeclampsia that have been used for decades. Methods of analysis have changed over time, but reference ranges may relate to historical data. An internet search of 100 laboratory test directories that listed reference ranges for UPC and/or 24UPE surveyed current reference ranges. Naming of the tests varied considerably, sometimes posing challenges for finding the tests. UP/C reference ranges were found in 65 directories and 8 directories had gender-specific ranges. Only 6 directories listed pregnancy-specific ranges. Upper limits of reference ranges for UP/C varied from 0.040-0.4 mg protein/mg creatinine. For 24hUPE, 99 directories listed the test and 94 had reference ranges. The upper limit of ranges varied from 40-300 mg/24h and 5 directories had pregnancy-specific ranges.

The survey found variation in test naming, test offerings, reporting units and reference ranges. Surveying laboratory directories provides a means to survey a variety of current laboratory practices. The wide variation of reference ranges raises questions about the validity of the ranges. Some PCR ranges probably are inappropriately low for female and elderly patients Directories rarely list decision levels for 24hUPE and UP/C during pregnancy and proteinuric disorders. Changes of assay methods and lack of data on aged populations raise questions about applying historical reference ranges for these tests. Harmonization of naming and methods and additional data about performance and reference ranges of current methods for urine protein quantification might benefit clinical practice.

Keywords: Proteinuria, Protein/creatinine ratio, Test naming

1. Introduction

Quantitative measures of urine protein excretion assist in detecting and monitoring renal disease. The glomerular filtration barrier normally excludes more than 99.9% of plasma protein from the glomerular filtrate Of the approximately 2 grams of protein that pass through the glomerular barrier, most is taken up in the proximal renal tubules. Studies from decades ago determined that healthy adults, consequently, excrete only about 100 mg of protein in urine daily[1,2] and up to a third of that is comprised of the Tamm Horsfall glycoprotein, also known as uromodulin, that is secreted by renal tubular cells[3]. Protein excretion increases with upright posture versus bedrest and

with exercise, fever and advancing age[1,2]. Laboratory analysis of urinary excretion commonly is performed as a 24-hour urine protein excretion (24hUPE) or as a urine protein/creatinine ratio (UP/C) on a random urine collection, where creatinine is used to correct for the highly variable volume of urine that is produced[4-10]. Measures of protein excretion are applied as indicators of preeclampsia during pregnancy[11-13] and to detect and monitor a variety of proteinuric disorders such as immunoglobulin A (IgA) nephropathy, minimal change disease, systemic lupus erythematosus and overflow proteinuria in multiple myeloma[14-19]. As an example, guidelines for IgA nephropathy identify a urine protein excretion of under 1 g/24h as a target for treatment[17] and proteinuria reduction has been accepted as a surrogate end point in treatment trials of IgA nephropathy[19].

The present survey of current laboratory practices examined whether information in laboratory test directories incorporated information from recent clinical guidelines for preeclampsia or other disorders. There also is a question about whether reference ranges should be updated. Reference ranges for 24UPE and UP/C were established decades ago using manual methods with different reagents and assay methods than in current use[1,2,8,20-26]. Most laboratories now employ dye-binding methods using pyrogallol red molybdate or pyrocatechol violet or turbidimetric methods using benzethonium salts as an aggregant[27-31]. Different methods react differentially with various urine protein components and often provide substantially different quantitative results[8,20-26]. Changes of assay methods and lack of standardization of assays raise questions about appropriate reference ranges and clinical decision levels. The present study examined current laboratory reference ranges for UP/C and 24UPE by surveying 100 laboratory test directories.

2. Methods

Google internet searches were performed in August and September 2024 using institution or country names together with “laboratory test menu,” “laboratory test directory,” and “laboratory reference ranges”. All information used is publicly available and no confidential patient or institutional data were accessed. Newsweek “best hospitals 2024” for the United States and the world were used as a guide to identify institutions to search for directories in English language. Additional medical school-affiliated hospitals and large referral laboratories also were searched. Test directories with reference ranges for UP/C and/or 24hUPE were found for 100 laboratories, representing about 60% of organizations searched. Reference ranges for a few laboratories were found in posted lists of reference ranges. Reference values for Dana Farber Cancer Center were accessed through the site for Massachusetts General-Brigham laboratories. Directories for some hospital laboratories represented core laboratories for a network of clinical sites including the hospital that was the initial search entry.

Search failures resulted from inability to find a test directory, test directories that were collection guides without reference ranges, access restrictions, lack of reference ranges for the tests of interest or reference ranges listed as “refer to chart” or “variable”. Failure to find some test directories possibly resulted from incorrect organizational search terms or from restricted access to directories.

3. Results

3.1. Internet Searches of Test Directories

Searches of more than 180 hospitals and referral laboratories found 100 test directories or reference range lists with reference ranges for PC/R and/or 24hUPE. The 100 test directories with reference ranges represented 8 laboratories in the United Kingdom, 6 in Canada, 2 in Australia, 2 in New Zealand, 1 in Ireland, 1 in Singapore and 80 in the United States. Most large referral laboratories had directories with additional interpretive information including reference ranges. Laboratories affiliated with academic medical centers more often had directories with reference ranges than medical centers without academic affiliations, although no test directories were found for some prominent academic medical centers. Some test directories may be limited to intranet access or, in some cases, search terms and strategies may have been insufficient. Finding some directories or lists of reference ranges involved several steps that included referral to a core laboratory site or selection of subdirectories “for providers” or specific laboratory sections such as chemistry or clinical biochemistry. Some searches required referral to a list of reference ranges. Most directories provided limited information about the specific test method for urine protein, sometimes providing a general descriptor such as “spectrophotometric” or “turbidimetric” or “colorimetric,” and rarely providing the specific vendor and type of method. Ten laboratories noted use of a pyrogallol red dye methods, two used a pyrocatechol violet dye methods, 25 used turbidimetric methods that were interpreted as methods using benzethonium chloride or specifically noted use of a benzethonium method and 1 laboratory listed a biuret method which probably is an erroneous entry.

3.2. Test Naming

Searching for the specific tests of interest posed a greater challenge than expected. Use of a search tool in directories often was unsuccessful due to variation in the naming of these tests with variable order and usage of descriptors such as “urine,” “total,” and “quantitative” and variable usage of abbreviations, commas, parentheses and dashes in test names that defeated finding test names using a search tool. A representative list of examples of test names for PC/R is shown in **(Table 1)** together with their frequency among the 100 directories sampled. Not all naming variations are listed. Names beginning with “Protein/Creatinine ratio” were most common, but some names began with urine, total, abbreviations or other terms. Entry of “protein” into search tools tended to provide a long list of possibilities. Most directories allowed an alphabetical search. Identifying the tests of interest often involved alphabetical searches under p, t or u for entries beginning with “protein,” “total,” or “urine.” Finding the entry for PC/R in one directory required searching for “creatinine” due to naming of the test, “Creatinine and protein, random urine” and this example or other directories with unusual naming practices may have led to failures to find a test.

Naming of tests for 24hUPE similarly had wide variation in naming of tests with some examples in **(Table 2)**. Variation in the initial term as “protein,” “total,” or “urine” complicated searches. One laboratory identified a test as specific for pregnancy. Some laboratories offered options for testing 12-hour specimens or, rarely, 6- or 8-hour specimens that are not included in the list.

3.3. Reference Ranges for UP/C

Reference Values for UP/C were expressed using several different units. Directories outside of the United States reported values as mg protein/mmol creatinine or g protein/mmol creatinine (a mmol of creatinine is equivalent to 113 mg of

creatinine). In the United States, 7 directories listed reference ranges as a ratio without units, 25 reported as mg protein/mg creatinine, 15 reported as mg protein/g creatinine and 1 reported as g protein/g creatinine. All values were converted to mg protein/mg creatinine for comparison. Only reference ranges for adults were considered. Most directories listed a single reference range for all ages, only 6 directories listed age-specific ranges pediatric ranges. Eight directories listed gender-specific reference ranges and eight directories listed a lower limit above 0. However, it is unclear what clinical value there is in defining a lower limit for protein excretion.

Table 1: Examples of the naming of tests for UP/C.

Directory Listing	Number of Directories
Protein/creatinine ratio, urine	10
Protein/Creatinine, Random Urine	7
Protein/Creatinine Ratio	7
Protein/Creatinine Ratio, Random Urine	6
Urine Protein/Creatinine ratio	5
Protein/Creatinine Ratio, Urine, Random	3
Total protein/creatinine ratio	4
Protein Random Urine	2
Creatinine and Protein, Urine Random	1
Orthostatic Proteinuria, random, urine (first void)	1
Pre-Eclampsia Protein/Creatinine ratio, urine	1
Protein and Creatinine, Random Urine	1
Prot/Crea Ratio, U	1
Protein:creatinine ratio, urine	1
Protein Excretion Urinary	1
Protein with Creatinine and Ratio, Random Urine	1
Protein, Urine	1
Protein, Urine, Random, with Creatinine	1
Protein, Quantitative, Random Urine	1
Protein, Quantitative, Random Urine Pregnancy	1
Protein to creatinine ratio	1
Protein-Urine, Random	1
Protein, Total, Urine	1
U Protein/creatinine ratio	1
TP CREAT RATIO (URINE)	1
Urine Protein & Creatinine, with ratio, Random	1
Urine, Random, Total Protein/Creatinine Ratio	1
Urine Total Protein and Creatinine Ratio	1

The upper limit of reference ranges for UP/C varied from 0.04-0.4 mg protein/mg creatinine **(Table 3)**. The value of 0.04 mg/mg was a significant outlier and other directories without specifying gender ranged from 0.10-0.40 mg/mg. Upper limits for gender-specific ranges for males ranged from 0.06-0.15 mg/mg and for females from 0.100-0.212 mg/mg **(Table 4)**. Ranges for females are expected to be higher than for males due to lower creatinine production, which lowers the denominator. Reference ranges for adults did not correct for age, although, with advancing age, there is a progressive decline of creatinine excretion and, also, possibly a slight increase of protein excretion. Six directories provided pregnancy-specific ranges with upper limits from 0.2 to 0.3 mg/mg. One directory named a test specifically as "Pre-Eclampsia Protein/Creatinine ratio, urine." Four directories listing UP/C tests did not provide a reference range for the ratio and, instead, listed a reference range for the component test for urine protein concentration. Upper limits varied from 12-26 mg/dL for the urine protein concentration. Only a few directories described the source of reference ranges. Unique values in 9 directories suggested that the ranges may have been derived from reference range studies by the laboratory, but directories did not describe the populations used to determine these ranges. The eight directories with gender-specific values had unique values that suggested performance of reference range studies by the laboratory. Two of these laboratories listed turbidimetric methods using benzethonium chloride and two listed methods as colorimetric which are presumed to be dye-binding methods. Ranges for the benzethonium method were slightly lower for this very small sample size.

Table 2: Examples of naming of tests for 24UPE.

Directory Listing	Number of Directories
Protein, 24Hour Urine	15
Protein, Urine 24 Hour	10
Protein, total, 24 hour urine	10
Protein, Total, Urine, 24 Hour	5
Total protein, 24 hr urine	7
Protein Urine Timed	6
Protein, Timed Urine	4
Protein (total), urine or Protein, total, urine	3
Protein (urine) or Protein urine	3
Urine protein, 24 hours	2
Protein, Quantitative, Urine	2
Protein, Quantitative, 24-Hour, Urine	2
Urine 24 Hour Protein	2
24Hr Protein, Urine	1
Protein, UR TM QN	1
Protein/24 h	1
Protein, Total, Quantitative, 24-Hour Urine	1
Protein, total, timed urine	1
PROTEIN, UR-TIMED	1
Protein, Quantitative, 24-Hour, Urine Pregnancy	1
Protein-Urine, 24 Hr, Urine, Quantitation	1
Total protein – Urine (24 hour)	1
Urine protein excretion	1
URINE TOTAL PROTEIN, 24 HR	1
Urine Protein, Total (Quant)	1

Table 3: Reference ranges in laboratory directories for UP/C without specified gender.

Upper limit(mg/mg)	Number of directories
0.04	1
0.10-0.12	4
0.12-0.14	3
0.15	16
0.16-0.19	10
0.20	16
0.25-0.27	3
0.39-0.40	5

4. Reference Ranges for 24hUPE

More directories, a total of 94, contained a test listing and reference ranges for 24hUPE than for UP/C. Values were

expressed as mg/24h, mg/d, g/24h or g/d. One laboratory had values expressed as mg/d/m^2 (adjustment for body surface area). One range listed as mg/L; it is unclear whether this is a misprint. Values were all converted to mg/24h for comparison. Four directories provided pregnancy-specific ranges. Two directories specified separate ranges for patients at bedrest or who are ambulatory. Two directories listed a 24hUPE test but provided a reference range only for urine protein concentration with an upper limit of 13.5 mg/dL and 150 mg/L, although it is unclear whether the latter could be a misprint intended to be 150 mg/d **(Table 5)**.

Table 4: Upper limits of gender-specific reference ranges for urine protein/creatinine ratio in 7 U.S. and 1 Canadian laboratory directories providing gender-specific ranges. Units as mg protein/mg creatinine.

Directory	Males	Females
US Hospital	0.060	0.100
US Reference Lab	0.68	0.107
US Hospital	0.070	0.105
US Hospital	0.110	0.160
US Hospital	0.110	0.160
US Reference Lab	0.148	0.184
Canadian Hospital	0.159	0.212
US Reference Lab	0.170	0.220

Table 5: Upper limits for reference ranges in laboratory directories for 24hUPE.

Upper limits (mg/24h)	Number of Directories
40	1
70-90	7
80 at bedrest	1
100	4
100 at rest	1
137-140	6
149-150	51
150 ambulatory	2
165	4
170-180	2
200	4
225-229	4
250	2
250 strenuous exercise	1
299-300	4
300 during pregnancy	5
Different units: mg/24h/m^2	
150	1
Upper limit as concentration	
13.5 mg/dL	1
150 mg/L (Misprint?)	1

The upper limit of reference ranges in directories varied from 40-300 mg/24h. The value of 40 mg/24h was an outlier and the next lowest value was 70 mg/d. About half of directories, a total of 51, listed an upper limit of 149 or 150 mg/24h. Few directories listed a source for the reference ranges provided.

Few directories provided a reference range for urine protein concentration due to the wide variation in the volume of urine excretion, often noting that no reference range is established. Therefore, a compilation of ranges was not performed. A few directories with listed ranges had upper reference limits varying from 10-25 mg/dL.

5. Discussion

A survey of laboratory test directories is one means of assessing current laboratory practices across many organizations. The original intent of this survey was to examine reference ranges for tests measuring urinary protein excretion. The wide variation in the naming of tests was an unexpected issue. However, multiple previous reports have described the lack of standardization of laboratory test names and the potential confusion and problems that can result[32-36]. Some ongoing efforts, such as TRUU-Lab[34], aim to improve standardization of laboratory test names. Development of tools such as LOINC provides some specificity in identifying tests[37], but those codes are not practical identifiers for test directories or for ordering test menus. The present survey of laboratory test directories describes examples of the problem of test naming for two tests assessing urine protein excretion that have been in use for several decades. Over that time, one would have hoped that some consensus could have been reached regarding naming of the tests, but that has not occurred. Some recommendations for naming practices have been proposed[32-36]. Rather than proposing guidelines that may have varying implementation, another possibility to consider would be to develop a dictionary of standard names for common laboratory tests.

The two tests, UPE and 24hUPE may serve as examples of how variation in test names increases when terms identifying the specimen type are included. A practical consequence of the variation of test names is difficulty in finding a test of interest in a test directory and this problem may be of increasing significance as more patients seek information about their test results. The observed variation in test naming also might illustrate the challenges for medical providers trying to order tests for assessing proteinuria, if test ordering menus do not include synonyms or better search tools for identifying tests of interest than are provided for test directories. Confusion about test naming can be one source of ordering the wrong test and errors in what sometimes has been called the pre-preanalytical process[38]. Test directories serve as a potential source to survey laboratory practices on test naming on a national and international scale, although the sampling likely is biased towards large laboratories versus small community hospital and clinic laboratories.

This survey of test directories shows wider availability of testing and reference ranges for 24hUP than for UP/C. That may limit the use of UP/C measurements in some organizations and suggests that use of 24hUPE remains more widespread.

Guidelines for diabetes care generally recommend testing of albumin/creatinine ratios rather than timed albumin or total protein excretion[39]. That is based on recognized difficulties with timed collections and greater analytical sensitivity and standardization of urine albumin assays versus measurements of total urine protein[10,16,39]. The variation of creatinine excretion related to gender and age impact albumin/creatinine ratios just as they do for UP/C, but, for the sake of simplicity, most guidelines have used single defined decision levels for both sexes and all adult ages. This approach is used by most laboratories for

UP/C as well. The transition from 24hUPE to UP/C appears to be less than for urine albumin measurements and many textbooks, websites and publications still refer to the 24hUPE is the "gold standard" for assessing urine protein excretion.[1, 2, 6-10] This designation is arguable, however, considering the high rate of inaccurately timed and incomplete 24-hour collections that justified the preference for albumin/creatinine ratios versus timed albumin excretion. Particularly during pregnancy when there is increased urinary frequency, the rate of incomplete 24-hour collections can approach 50%.[11] Use of a 12-hour collection is another alternative,[13] and a few directories list separate tests for 12-hour urine protein.

Urine protein excretion in adults is commonly described as less than 150 mg/24[1,2]. This value appears to be adopted by about half of laboratories surveyed and is listed as the upper limit in 2002 guidelines[4,5]. Lower values for upper limits of reference ranges in some directories might represent population-derived reference ranges, such as a mean ± 2 standard deviations, while other values listed as reference ranges may represent clinical decision levels or published ranges. The upper reference limit of 150 mg/24h is based on studies from decades ago that have several limitations[1,2]. An example of primary data from studies in the 1960s found excretion of 40-69 mg protein/24h at rest and 5- to 10-fold higher excretion in 20 men after running a marathon[21]. A summary of 9 early reference range studies found mean 24UPE to vary considerably depending on the study and method of analysis from 29 to 216 mg/24 in different studies[22]. Studies had small numbers of young adults as subjects (largest number 49 subjects). Another study of 88 young adults found a normal range of 82-207 mg/24h[23]. A 1987 study of 43 subjects found a range of 24hUPE from 11-115 mg/24h[25]. A study published in 1990 of 30 young men and 30 women found ranges of 40-147 mg/24h for men and 28-131 mg/24h for women[27]. Generally, studies showed slightly higher 24hUPE for men than for women. Historical studies used to establish reference ranges had small numbers of subjects and studies lacked elderly subjects. Also, methods of analysis differed from current methods. Nevertheless, reference ranges for 24hUPE for most laboratories appear to be based on historical data and extensive reference range studies for 24hUPEare unlikely to occur for most laboratories due to the challenge in obtaining 24-hour urine collections. Although historical ranges are widely used by laboratories, there are reasonable questions about whether reference ranges used by laboratories are appropriate for current methods and for application to elderly patients. Generally, it has been stated that urinary protein excretion increases with age although that could relate to an increased burden of chronic kidney disease in the elderly[1,2].

Early studies of UP/C found upper limits of reference ranges of 0.11-0.20 mg/mg[24-26]. These studies of young adults used different methods for protein analysis than current laboratory methods. Two more recent studies that used a dye-binding method, (pyrogallol red molybdate) in current clinical use examined larger populations. The AusDiab Study analyzed specimens from more than 10,000 subjects and 97.6% of specimens had UP/C <0.2 mg/mg.[40] This study of a cross-section of adult Australians included some individuals with diabetes and substantial proteinuria, so it is not ideal as a reference range study. A study of UP/C for more then 1,300 Chinese adults found that the upper 95% population limit ranged from 0.122 mg/mg for young men to 0.160 mg/mg for men over 60 years of age and from 0.136 for young women to 0.223 for women over 60 years of age.[41] That study clearly illustrated the effects of gender and age on UP/C values, which are expected based on changes in creatinine excretion with age and gender. One early study suggested correction for estimated daily creatinine excretion with the formula:

Creatinine (g/d) = (140 – Age) X (Weight in kg)/5000. And multiply by 0.85 for women[24] the small number of directories that have gender-specific reference ranges and that appear to be determined from in-house reference range studies, had slightly lower ranges than the AusDiab study. Such laboratory-specific studies may lack inclusion of elderly subjects. None of the surveyed directories adjusted reference ranges for adult age. The two studies using current dye-binding assays, support an upper limit of reference ranges of about 0.2 mg/mg, although gender and age-specific reference ranges probably should be considered, especially if elderly patients are being tested. There is a lack of similar primary data on reference ranges for widely-used turbidimetric methods using benzethonium salts. Studies suggest that dye binding methods react with low molecular weight peptide components that are not measured by benzethonium methods[31] and dye-binding and turbidimetric methods appear to have differential reactivity with different urinary protein components[28,31]. Benzethonium methods have been reported to provide 10-20% lower results than dye-binding methods[8]. Current methods appear to have low reactivity with the Tamm-Horsfall glycoprotein, possibly due to its very high carbohydrate content[28].

During pregnancy there is a substantial increase in urine protein excretion and even greater when there are twins[11]. Primary data show upper 95% confidence limits of 200 mg/24h and 259 mg/24h in two studies.[42, 43] For many years, guidelines from the American College of Obstetrics and Gynecology, World Health Organization and International Society for Study of Hypertension in Pregnancy all have recommended a cutoff of 0.3 g/24h (300 mg/24h)[12]. A quoted summary of the evidence for this cutoff value is as follows: "Although this threshold is widely accepted for defining abnormal protein excretion, its origin does not seem to be based on clinical outcomes but rather on expert opinion and small studies that have attempted to establish statistically normative values for pregnancy"[11]. Urine protein excretion rather than albumin excretion continues to be applied as an indicator of preeclampsia in pregnancy, but a limited number of directories listed the cutoff recommended by guidelines. Use of UP/C with a cutoff of 0.3 mg protein/mg creatinine also has been recommended[11], but, again, was rarely included in directories. The homogenous gender and age range of pregnant adults avoids the need to correct for age and gender for diagnostic cutoff for UPC.

Guidelines have established several decision levels for 24hUPE or UP/C besides those applied to pregnancy, but this information is rarely included in test directories. The National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) in 2008 recommend that cutoff values of 50 and 100 mg/mmol, respectively (0.44 and 0.88 mg/mg) should be used to identify significant proteinuria[8]. Except in the case of pregnancy, quantitative tests for urine protein excretion usually are not used as screening tests but are ordered only when there is clinical suspicion of a renal

disorder or a diagnosis has been established. Then, the tests are used for monitoring. Quantitative protein measurements may be used to further assess proteinuria when urine dipstick tests show increased protein and the threshold of those tests corresponds to a PC/R of about 0.5 mg/mg,[6, 10] The marked increase of urine protein excretion with glomerular disorders, up to 100-fold or more above normal values, sometimes leads to decision levels substantially above population-based reference levels. Clinical guidelines for proteinuric disorders have established varying decision levels for different disorders such as minimal change disease, systemic lupus erythematosus and IgA nephropathy that are substantially above laboratory reference ranges[16,17]. A treatment target for IgA nephropathy, for example has been identified as < 1,000 mg/24h[17]. Information about guideline recommendations rarely is included in test directories.

High between-laboratory variation in test results for urine protein measurements on the same specimen have been seen on quality assurance programs[8,30,44]. That poses a potential problem in trying to apply a fixed historical reference ranges or specific clinical decision level for evaluation of preeclampsia or proteinuric disorders and that problem appears to be largely ignored in clinical guidelines. Variation in calibration material may be a factor in between-laboratory differences as well as methodological differences[8,26-30]. A practical consequence is that serial monitoring of proteinuric disorders over time should be performed using a test method from the same vandor and, preferably, by the same laboratory. Standardization of the methods for urine protein measurement sometimes has been claimed to be an impossible task considering the lack of a standard reference material and variable composition of urine protein. However, clinical application of these tests might benefit from improved harmonization and additional reference range data or decision levels with current methods, rather than relying on historical values that appear to be in common use. Limited reference range data on elderly populations appears to be a significant gap, considering the increasing incidence of chronic kidney disease with age. Optimal reference ranges, particularly when applying UP/C measurements to an elderly population, appear to benefit from adjustment for gender and age due to substantial changes in creatinine excretion with age and gender. Reference ranges for UP/C for many laboratories may have an inappropriately low upper limit for application to an elderly population. Gender and age have lesser impact on 24hUPE, but there appear to be limited data regarding effects of advanced age on reference ranges for this test and data with current analytical methods are limited.

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