ACCU | REFERENCE MEDICAL LAB®

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URINARY TRACT INFECTION MOLECULAR TEST PANEL

Real-Time Polymerase Chain Reaction

URINARY TRACT INFECTION (UTI) IS ONE OF THE MOST COMMON HUMAN BACTERIAL INFECTIONS

PATIENTS ARE OFTEN MISDIAGNOSED WITH A 'BLADDER SYNDROME'

IN ATTEMPT TO EXPLAIN THEIR CONTINUED UTI SYMPTOMS

26-44%

WILL HAVE A UTI RECURRENCE **WITHIN 6 MONTHS**

ONE in 10 girls and **ONE** in 30 boys

DEVELOPING A UTI BEFORE THE AGE OF 16

ONCE ESTABLISHED, CHRONIC UTI (cUTI) AND RECURRENT UTI (cUTI)

CANNOT BE ERADICATED WITH SHORT-TERM ANTIBIOTICS

DIAGNOSTIC TESTS FOR UTI HAVE BEEN WIDELY DISCREDITED IN PEER-REVIEWED PUBLICATIONS

FOR OVER 30 YEARS

7 OUT OF 10

DON'T BELIEVE THEIR UTI TREATMENT WILL WORK

AT LEAST HALF OF ALL WOMEN WILL DEVELOP A UTI IN THEIR LIFETIME,

WITH **20-30%** GOING ON TO EXPERIENCE A RECURRENCE AND A SIGNIFICANT SUBSET DEVELOPING A CHRONIC FORM OF UTI

LEFT UNTREATED,

cUTI CAUSES ONGOING, **DEBILITATING AND LIFE-CHANGING SYMPTOMS**

7 MILLION

FEMALES EXPERIENCE A UTI EACH YEAR IN THE USA

UP TO 30% OF PATIENTS ACCORDING TO CURRENT GUIDELINES **WILL FAIL TO RESPOND TO TREATMENT**

80% **OF cUTI SUFFERERS** ARE FEMALE, IT IS ESPECIALLY **PREVALENT AMONG ELDERLY WOMEN** WHERE IT IS NOT ONLY CRUEL AND DEBILITATING, BUT ALSO LIFE-THREATENING

URINARY TRACT INFECTION MOLECULAR TEST PANEL
by Real-Time Polymerase Chain Reaction

What is UTI?

Urinary Tract Infection (UTI) is the general term for an infection occurring anywhere in the urinary system. Most UTIs involve the bladder and the urethra, but some can also involve the ureters and even the kidneys.

It is quite common for UTIs to be misdiagnosed, and this places an extreme and unnecessary burden on the healthcare system and the healthcare economy. Over 150 million people worldwide will experience UTIs annually, with females four times more likely to get them than males. In fact, at least half of all women will get a UTI during their lifetime, and a third of these occur before the age of 24. A compounding factor is that approximately 25% of all patients will experience a reoccurrence within six months, in some cases developing a chronic form of urinary infection.

Children are also prone to UTIs, with one in 10 girls and one in 30 boys developing the infections before the age of 16. Chronic UTI (cUTI) is a largely misunderstood form of the disease that is particularly difficult to diagnose and treat under current guidelines. Chronic UTI is especially prevalent among elderly women, for whom it is not only painful and debilitating, but can also be life-threatening.

Data shows that UTIs are increasing due to multidrug-resistant pathogens that are spreading globally from the over-prescription and widespread use of broad-spectrum antibiotic therapy instead of a more controlled approach which would match the optimal antibiotics to specific pathogens. Ironically, it can be said that the very treatment of UTIs with broad-spectrum antibiotics has itself become a major contributing factor to its global spread.

Molecular UTI Panel by ACCU Reference offers an extremely fast turnaround time and far more sensitive identification of bacterial species than all other testing methods, which allows for diagnoses and treatment that are narrowly matched to appropriate antibiotic choices.
The ACCU Reference Urinary Tract Infection Molecular Test Panel simultaneously identifies, from a single specimen, 17 pathogens (gram positive, gram negative and fungi) that are most commonly associated with UTIs.

GRAM NEGATIVE ORGANISMS	Acinetobacter baumannii Citrobacter freundii Enterobacter aerogenes Enterobacter cloacae Escherichia coli Klebsiella oxytoca	Klebsiella pneumoniae Morganella morganii Proteus mirabilis Proteus vulgaris Providencia stuartii Pseudomonas aeruginosa
GRAM POSITIVE ORGANISMS	Enterococcus faecalis Enterococcus faecium	Staphylococcus saprophyticus Streptococcus agalactiae
FUNGI	Candida albicans	

Next day turnaround and accurate detection of urinary tract pathogens provides the clinician with the critical information for more focused therapy and improved outcomes.
Based upon published recommendations, use of the appropriate narrow spectrum antibiotic in treating UTIs reduces the incidence of treatment failure. Rapid diagnostic molecular methods can allow for earlier intervention and optimized therapy when appropriate.

ABOUT CHRONIC UTI

Chronic Urinary Tract Infection (cUTI) is a largely under-diagnosed condition that affects a significant percentage of the population. The majority of those living with an undiagnosed and untreated cUTI are women.

Anyone can develop cUTI, and researchers suggest that the most significant risk factor for an cUTI is having been diagnosed with a UTI previously. Between 20–30 percent of all patients treated for an acute UTI are not fully cured and go on to develop a complicated, embedded infection which is extremely difficult to diagnose and treat.

When patients experience UTI symptoms but their tests say otherwise, there is a good reason to question those tests. Since the 1980s, peer-reviewed research has shown that MSU cultures (used by labs to diagnose UTIs) miss at least 50 percent of the infections for which they test. Urinary dipsticks (commonly used in the clinic or doctor's office to screen samples) are even less effective and have been known for at least a decade to be completely unreliable in ruling out infections.

URINARY DIPSTICK TEST

Today, dipsticks are often the first diagnostic tool GPs use to confirm an infection. These tests look for signs of infection, such as white blood cells (leucocytes or pus cells), blood, pH levels and nitrites. Although they are useful in confirming a clearly positive diagnosis, studies in the early 1990s concluded that **they are highly insensitive and unreliable at excluding infection in most clinical settings.** About a decade later, another team of researchers comprehensively studied the reliability of urinary dipsticks and determined that these first-line screening tests were not up to the job of excluding significant UTIs. It found dipsticks identified white blood cells just 55 percent of the time, and nitrites (another positive indicator of infection) only 10 percent of the time. A negative result offers no useful information in ruling out a UTI. **Given the proven shortcomings of urinary dipsticks, physicians should be extremely cautious when relying on this test to rule out a UTI.**

MID-STREAM URINE CULTURES

MID-STREAM URINE CULTURES (MSU) cultures are considered the gold standard for diagnosing UTI and have been in use since the late 1950s. **For over 30 years, researchers have warned of serious deficiencies that lead to these tests missing at least 50 percent of infections.** Studies have been repeated and calls for the abandonment of MSU culturing have been heard repeatedly, but these warnings have been ignored, and MSU culturing remains the main diagnostic tool for UTIs around the world.

PANEL DETAILS

TEST ORDERING CODE	**6300**
METHODOLOGY	**Real-Time Polymerase Chain Reaction (PCR).**
SPECIMEN REQUIREMENTS	**Clean catch urine specimen.**
MINIMUM VOLUME	**1.0 ml**
TEMPERATURE	**Refrigerated 7 days**
STABILITY	**Room temperature 24 hours**
TURNAROUND TIME	**1 business day. Susceptibility will follow.**

NOTES:

*** Proper sample collection is critically important for test accuracy.**

**** The patient should not have urinated for at least an hour before the urine specimen is collected.**

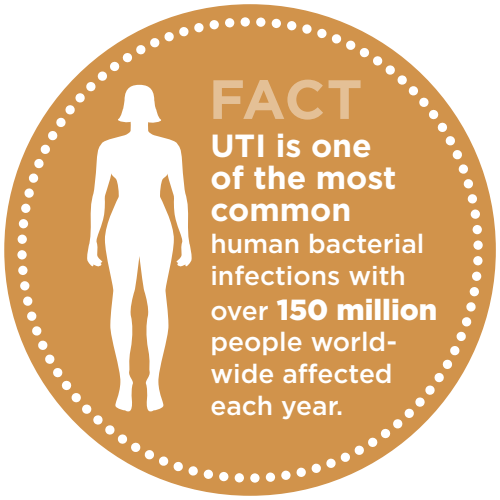
***** Send urine in a sterile container to Accu Reference Medical lab.**

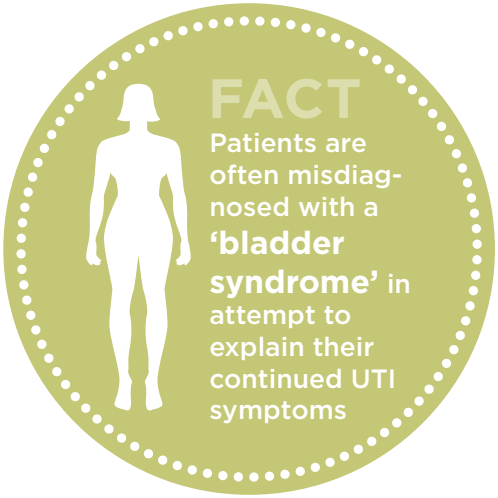
CLINICAL BENEFITS

- **Same day results**
- **Identifies bacteria regardless of recent antibiotic use**
- **Identifies difficult to culture pathogens**
- **Offers simplicity and convenience of single specimen collection**
- **Yields > 95% analytical sensitivity and specificity**
- **Identifies of 17 pathogens from a single specimen**

INDICATIONS FOR MOLECULAR UTI PANEL

- **Recurring UTIs**
- **Interstitial cystitis**
- **Pyelonephritis**
- **Pregnancy**
- **Over 50 years of age**
- **Chronic pain care patients**
- **Immunocompromised patients**





ADVANTAGES AND CHALLENGES OF THE MOLECULAR UTI TEST

ADVANTAGES

A molecular assay is highly sensitive, which helps indentify slow growers in urine samples which would otherwise take more than 48 hours.

Turnaround time for the Molecular UTI test is 5 hours.

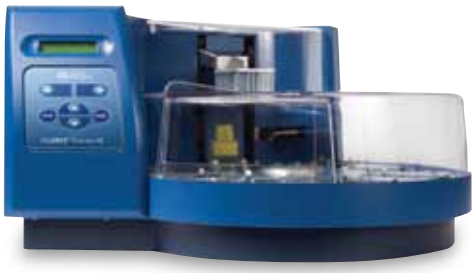
CHALLENGES

Increasing multidrug resistance in uropathogens is leading to high recurrence rates of UTI's and has become a global challenge for antibiotic treatment regimens.
It is extremely important to accurately identify the causative uropathogens for effective use of antibiotics.

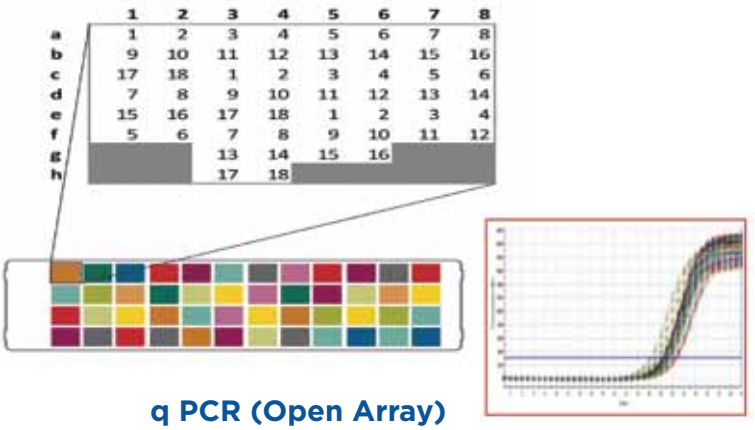
WORK FLOW OF OPEN ARRAY VERSUS URINE CULTURE

MOLECULAR UTI TEST

TEST RESULTS IN **5 HOURS**



DNA extraction using MagMAX



q PCR (Open Array)

URINE SPECIMEN

CONVENTIONAL CULTURE

TEST RESULTS IN **48 HOURS**

Culture on selective media for identification of gram negative and gram positive bacteria

Gram stain to confirm by morphology

Re-incubate for slow growers

SPECIMEN COLLECTION

Proper sample collection is critical for assuring the accuracy of the Molecular UTI test. Clean, uncontaminated specimens help to eliminate false positives and significantly boost the accuracy of results.

ACCU Reference Medical Laboratory believes that providing our medical professionals with the highest quality supplies, results in a better overall patient experience. We therefore offer medical practices, clinics and hospitals only the finest accessories, specimen collection kits and transporting supplies.

SPECIMEN CONTAINERS

ACCU Reference Medical Laboratory provides US manufactured, sterile, 90 mL specimen containers with labels. The jars are of the highest quality, leak proof and are fully certified for use in hospital pneumatic systems and approved for airline transport.

FEMININE URINE COLLECTION KITS

AccuFem is the first female urine collection device of its kind. The innovative, patented urine collection system was exclusively designed by ACCU Reference experts to offer women of all ages unparalleled comfort, convenience and privacy. The AccuFem Kit contains a plastic funnel shaped to fit the unique contours of the female body. Prior to use, the funnel is screwed onto a sterile plastic container and forms a spill-proof, tight seal. In addition, the AccuFem funnel has a convenient handle which makes the device easy to use for patients and attending medical personnel alike.

With AccuFem, urine is funneled directly into the container without the need to transfer the specimen from cups or toilet hats, which dramatically decreases spillage, specimen contamination, resulting false positives, and increases test accuracy and workplace hygiene.

The AccuFem Kit is designed for use by all patients, but is especially convenient for pregnant, obese, blind, elderly women, those with orthopedic problems, balance issues, as well as the mentally ill. Using AccuFem is completely intuitive and requires no special training.

CASTILE SOAP TOWELETTES

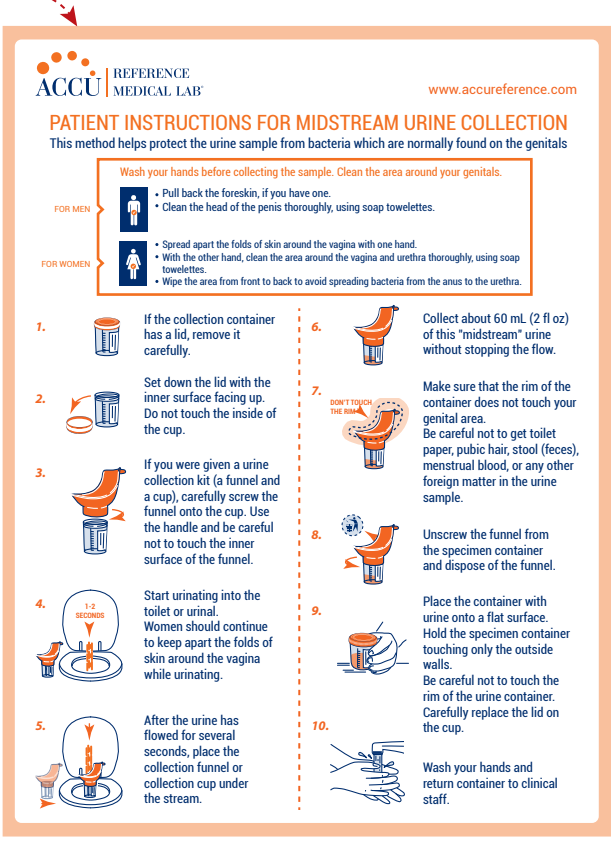
Castile Soap Towelettes are pH-balanced and saturated with a 2% coconut oil-based soap solution. Castile soap is gentle and often used for general cleaning, as well as surgical preparation. These individually packaged single use 5”x7” towelettes are ideal for midstream clean catch urine specimen procedures as well as general cleaning and personal hygiene.

SPECIMEN CONTAINERS DISPENSERS

ACCU Reference’s custom designed dispenser stores a typical office’s full day’s supply of 21 90ml containers which are conveniently dispensed one at a time. The dispenser takes up very little desktop space and can be mounted under wall cabinets or directly on almost any wall surface.
Loading the dispenser takes less than half a minute and will keep busy offices organized and tidy.

STEP BY STEP ILLUSTRATED INSTRUCTIONS

ACCU Reference provides easy to read patient instructions specifically written for your both female and male patients. Printed on repositionable vinyl film, the clearly explained instructions can be attached to any surface. Instructions can be translated into a number foreign languages upon request.



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PATIENT INSTRUCTIONS FOR MIDSTREAM URINE COLLECTION

This method helps protect the urine sample from bacteria which are normally found on the genitals

Wash your hands before collecting the sample. Clean the area around your genitals.

FOR MEN
- Pull back the foreskin, if you have one.
- Clean the head of the penis thoroughly, using soap towelettes.

FOR WOMEN
- Spread apart the folds of skin around the vagina with one hand.
- With the other hand, clean the area around the vagina and urethra thoroughly, using soap towelettes.
- Wipe the area from front to back to avoid spreading bacteria from the anus to the urethra.

1. If the collection container has a lid, remove it carefully.
2. Set down the lid with the inner surface facing up. Do not touch the inside of the cup.
3. If you were given a urine collection kit (a funnel and a cup), carefully screw the funnel onto the cup. Use the handle and be careful not to touch the inner surface of the funnel.
4. Start urinating into the toilet or urinal. Women should continue to keep apart the folds of skin around the vagina while urinating.
5. After the urine has flowed for several seconds, place the collection funnel or collection cup under the stream.
6. Collect about 60 mL (2 fl oz) of this “midstream” urine without stopping the flow.
7. Make sure that the rim of the container does not touch your genital area. Be careful not to get toilet paper, pubic hair, stool (feces), menstrual blood, or any other foreign matter in the urine sample.
8. Unscrew the funnel from the specimen container and dispose of the funnel.
9. Place the container with urine onto a flat surface. Hold the specimen container touching only the outside walls. Be careful not to touch the rim of the urine container. Carefully replace the lid on the cup.
10. Wash your hands and return container to clinical staff.

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Acc# **0000000000**

Phys: **John Doe, MD**

Patient: **Jane Doe**
DOB. 06/12/1981
Phone: (000) 000-0000
ID#: 00000000000
Route#:
Fasting: N

Age: 36
Sex: F
Room#
Page: 1

Coll. Date:01/23/18
Coll. Time:12:00 PM

Recv. Date: 01/23/18
Recv. Time: 04:12 PM

First reported on: 01/23/18
Final report date: 01/23/18

Print Date: 01/24/18
Print Time: 12:38

Test Name	Normal	Out of Range	Normal Range	Units
Report Status: FINAL				
URINARY TRACT INFECTION PANEL, PCR				
URINARY TRACT INFECTION			*Tech:VERON Date:01/23/18 16:13*	
Acinetobacter baumannii	NOT DETECTED		NOT DETECTED	
Citrobacter freundii	NOT DETECTED		NOT DETECTED	
Enterobacter aerogenes	NOT DETECTED		NOT DETECTED	
Enterobacter cloacae	NOT DETECTED		NOT DETECTED	
Enterococcus faecalis	NOT DETECTED		NOT DETECTED	
Enterococcus faecium	NOT DETECTED		NOT DETECTED	
Escherichia coli		**DETECTED**	NOT DETECTED	
Klebsiella oxytoca	NOT DETECTED		NOT DETECTED	
Klebsiella pneumoniae	NOT DETECTED		NOT DETECTED	
Morganella morganii	NOT DETECTED		NOT DETECTED	
Proteus mirabilis	NOT DETECTED		NOT DETECTED	
Proteus vulgaris	NOT DETECTED		NOT DETECTED	
Providencia stuartii	NOT DETECTED		NOT DETECTED	
Pseudomonas aeruginosa	NOT DETECTED		NOT DETECTED	
Staphylococ.saprophyticus	NOT DETECTED		NOT DETECTED	
Streptococcus agalactiae	NOT DETECTED		NOT DETECTED	
Candida albicans	NOT DETECTED		NOT DETECTED	

COMMENT:

This test was developed and its performance characteristics determined by Accu Reference Medical Laboratory. It has not been cleared or approved by the Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Approved by A.Seth, Ph.D.

---------- END OF REPORT ----------

Laboratory Director: Martin King, Ph.D.

Indentification of UTI pathogens using an open array platform on the *QuantStudio 12K Flex* system

Dr. Anjali Seth, Ph. D, DABCC

BACKGROUND:

Increasing multidrug resistance in uropathogens is leading to high recurrence rates for UTIs and has become a global challenge for antibiotic treatment regimens. It is extremely important to promptly and accurately identify the causative uropathogens for effective UTI management. We have custom designed an open array for rapid identification of 17 uropathogens using real time PCR technologies. The design of our urinary tract infection pathogen panel open array (UTI pathogen panel) allows testing of 48 urine samples for 17 targeted genes within five hours. DNA is extracted directly from urine samples and amplified on the Thermofisher QuantStudio 12k Flex open array system for detection of the following uropathogens; Acinetobacter baumannii, Klebsiella pneumonia, Citrobacter freundii, Morganella morganii, Enterobacter aerogenes, Proteus mirabilis, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella oxytoca, Proteus vulgaris, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus saprophyticus, Streptococcus agalactiae, Candida albicans.

OBJECTIVES:

To evaluate the UTI pathogen panel for its analytical performance characteristics and utility for patients at Accureference Medical laboratories. The real time PCR assay on the open array was compared with the currently performed traditional microbiology techniques, and its performance characteristics were evaluated.

METHODS:

A total of 124 urine specimens submitted for detection of UTIs by standard microbiology techniques were used for correlation studies using our UTI pathogen panel. Extraction of nucleic acids directly from urine specimens was performed using the Thermofisher MagMAX Multi sample Ultra kit on the Magmax automated extractor.
Identification of uropathogens was performed on the QuantStudio 12k flex using an open array system.

RESULTS:

Urine specimens (n=124) submitted to the microbiology laboratory for culture were tested in parallel for the presence of uropathogens using our UTI pathogen panel. A total of 90/124 specimens were identified as positive for uropathogens using the UTI panel whereas only 75 of these specimens were resulted as positive for any uropathogen by microbiology. There was 100% concordance with culture results for these 75 specimens but in 22/75 specimens (29%), at least one additional pathogen undetected by culture was identified using the UTI panel. The most frequent organisms identified in the positive specimens were E.coli followed by Klebsiella pneumonia and Enterococcus faecalis. Analytical sensitivity of PCR reactions for detection of the pathogens was determined by making standard curves on bacterial isolates and appropriate cut-off values were applied to correlate with bacterial loads of 103 colony, forming units (CFU) per ml. The panel showed 100% specificity in identification of uropathogens in our studies.

CONCLUSIONS:

The UTI pathogen panel offers the advantage of identifying the cause of UTI within hours and is more sensitive than traditional microbiology methods. The panel helps to reduce the turnaround time for identification of slow growing and fastidious UTI pathogens. The molecular based semi quantitative UTI pathogen panel is a good alternative to traditional microbiology methods for sensitive and specific detection of uropathogens.

COMMON DIAGNOSES FOR MOLECULAR UTI TEST

N30.00	Acute cystitis without hematuria
N14.0	Analgesic nephropathy
R82.71	Bacteriuria
N20.0	Calculus of kidney
N20.2	Calculus of kidney with calculus of ureter
N71.1	Chronic inflammatory disease of uterus
N11.9	Chronic tubulo-interstitial nephritis, unspecified
N30.90	Cystitis, unspecified without hematuria
N42.9	Disorder of prostate, unspecified
R30.0	Dysuria
N18.6	End stage renal disease
N73.9	Female pelvic inflammatory disease, unspecified
R50.9	Fever, unspecified
N14.1	Nephropathy induced by other drugs, medicaments and biological substances
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance
N34.1	Nonspecific urethritis
R82.99	Other abnormal findings in urine
R82.79	Other abnormal findings on microbiological examination of urine
N28.89	Other specified disorders of kidney and ureter
N76.89	Other specified inflammation of vagina and vulva
A41.9	Sepsis, unspecified organism
N14.4	Toxic nephropathy, not elsewhere classified
R82.90	Unspecified abnormal findings of urine
N05.2	Unspecified nephritic syndrome with diffuse membranous glomerulonephritis
N05.1	Unspecified nephritic syndrome with focal and segmental glomerular lesions
N05.0	Unspecified nephritic syndrome with minor glomerular abnormality
N05.9	Unspecified nephritic syndrome with unspecified morphologic changes
N34.3	Urethral syndrome, unspecified
N20.9	Urinary calculus, unspecified
N39.0	Urinary tract infection, site not specified

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