UTI, DELIRIUM, AND DEMENTIA: A CONCEPTUAL BIOINFORMATICS FRAMEWORK FOR CLINICAL ATTRIBUTION

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ABSTRACT

Urinary tract infection (UTI) is frequently invoked to explain delirium, confusion, and functional decline in persons with dementia. Yet urine positivity in this population often reflects asymptomatic bacteriuria, colonization, chronic pyuria, contamination, or sampling noise rather than clinically attributable infection. For biomedical informatics and computational diagnostics readers, this narrative review contributes an integrative conceptual bioinformatics framework for probabilistic clinical attribution of suspected UTI in dementia under uncertainty.We formalizes the attribution problem by distinguishing organism detection from a clinically plausible infection-related contribution to neurocognitive decline. The framework integrates clinical, laboratory, biological, and longitudinal data to clarify whether urinary findings are clinically attributable, potentially contributory, incidental, or misleading. As a secondary contribution, we propose a five-layer implementation blueprint comprising clinical phenotype capture, conventional laboratory data, host-response and omics data, computational inference, and decision-support outputs. This architecture is offered as a translational scaffold for future development and validation, not as an established diagnostic platform. The review also outlines a research agenda for future framework validation and refinement.

KEYWORDS

Urinary tract infection; Dementia; Delirium; Asymptomatic bacteriuria; Bioinformatics; Neuroinflammation; Precision metagenomics; Machine learning

1. INTRODUCTION

Urinary tract infection (UTI) occupies a paradoxical position in dementia care. It is common enough to demand clinical attention, dangerous enough to require timely treatment, and treatable enough that delayed recognition can carry meaningful consequences. Yet it is also one of the most frequently over-attributed explanations for acute cognitive or functional decline in older adults [1].

The diagnostic challenge is that dementia weakens the usual symptom anchors of UTI. Patients may be unable to clearly report urinary pain, urgency, suprapubic discomfort, or flank tenderness. Clinicians are therefore left interpreting nonspecific changes such as agitation, reduced intake, falls, immobility, sleep disruption, or delirium. These changes may reflect infection, but they may also arise from dehydration, constipation, medication effects, metabolic instability, pain, environmental transition, neurologic events, or dementia progression. The central question is not whether UTI can worsen cognition. It can. The harder question is whether urinary findings are clinically attributable to the acute change, potentially contributory, incidental, or misleading.

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Urine testing further destabilizes the diagnostic process because positive findings are common in older adults even when no symptomatic infection is present [2]. Bacteriuria and pyuria therefore function poorly as stand-alone evidence of UTI in this population. For this reason, asymptomatic bacteriuria should generally not be treated in older adults unless a narrow clinical exception applies [3].The problem is magnified in advanced dementia, where diagnostic uncertainty often leads to treatment despite weak clinical support. Only a small minority of suspected UTI episodes in advanced dementia meet minimum criteria for antibiotic initiation, yet most episodes that fail to meet those criteria are still treated [4]. Positive urine findings are also common whether or not clinical criteria are satisfied. The implication is straightforward: “confusion plus positive urine” is not a diagnosis of UTI. It is an uncertain signal that must be interpreted against symptoms, host risk, competing causes, and clinical trajectory.

A more defensible approach begins by separating clinical instability from diagnostic uncertainty. When physiologic instability suggests invasive infection or sepsis, treatment should not be delayed. When the patient is stable, urinary findings should be interpreted through a structured diagnostic sequence that first asks whether the clinical syndrome is plausibly urinary, then uses urinalysis as a screen, culture as confirmation, and follow-up review to support escalation or de-escalation as new information emerges [5].This framing is important because the literature is not simple. Systematic reviews support an association between UTI and delirium in older adults, but the evidence linking nonspecific confusion to UTI is much weaker. One recurring limitation is that many studies do not clearly separate symptomatic infection from bacteriuria or asymptomatic bacteriuria [6,7]. The biologically plausible claim is therefore narrow but important: UTI can contribute to delirium, but a positive urine result does not establish causality in an individual patient.

The unresolved problem is attribution. In cognitively impaired older adults, confusion, functional decline, reduced mobility, or behavioral change may prompt urine testing even when a urinary source is uncertain. Direct evidence from advanced dementia and geriatric populations shows that diagnostic uncertainty can lead to antibiotic treatment despite weak clinical criteria [4]. Evidence from fungal UTI, diabetes-associated UTI, and renal transplant complicated UTI [8–10] is considered here only as indirect translational evidence concerning complex host states, microbial ecology, and antimicrobial resistance; it does not directly validate UTI attribution in dementia.

This review’s primary contribution is an integrative conceptual bioinformatics framework for probabilistic clinical attribution of suspected UTI in dementia under uncertainty.The primary audience is biomedical informatics and computational diagnostics researchers, with secondary relevance for geriatric medicine, infectious disease, clinical microbiology, and antimicrobial stewardship.Its secondary contribution is a five-layer bioinformatics architecture that specifies how clinical, laboratory, biological, computational, and decision-support domains could be organized for future implementation. It does not present a validated diagnostic decision model, clinical calculator, or deployable clinical decision-support system. Rather, it defines the scientific and interpretive structure that future attribution tools must satisfy. Afuture research agenda for validating dementia-specific UTI attribution models is provided.

2. NARRATIVE REVIEW METHODOLOGY

This narrative review is organized around a single translational problem: how suspected UTI in dementia can be transformed from a urine-positive label into a clinically interpretable attribution estimate under uncertainty. A narrative review design is appropriate because the question addressed here is not limited to a single intervention, exposure, or pooled effect estimate. Rather, the problem requires synthesis across geriatric infectious disease, delirium biology, neuroinflammation, urinary microbiome science, molecular diagnostics, antimicrobial

stewardship, machine learning, and clinical decision support. In this setting, the central issue is not simply whether urine testing detects microorganisms. The more consequential question is whether urinary findings can be interpreted within the clinical pathway in which delirium, functional decline, antibiotic exposure, and diagnostic uncertainty are produced.

This review therefore uses a structured narrative approach rather than a systematic review or meta-analysis. Narrative reviews are useful when the literature spans heterogeneous mechanisms, populations, study designs, and implementation contexts, particularly when the goal is conceptual integration rather than quantitative effect estimation [11-14]. To preserve interpretive rigor, evidence was organized by clinical function and proximity to the dementia-UTI attribution problem. Studies conducted directly in older adults, long-term care residents, advanced dementia populations, or delirium cohorts were treated as the most clinically proximate evidence. Studies of urinary microbiome structure, host-response biomarkers, molecular diagnostics, diabetes-associated UTI risk, fungal urinary disease, antimicrobial resistance, and next-generation sequencing were used to identify biologically plausible variables that may improve attribution. Computational and knowledge-graph literature was used to support framework development, not to imply that any specific algorithm has already been validated for UTI attribution in dementia.

2.1. Search Strategy, Eligibility, and Evidence Prioritization

The literature search focused on peer-reviewed sources indexed in PubMed/MEDLINE and PubMed Central and included English-language literature published from January 2000 through June 2026. Reference lists from key guidelines, systematic reviews, and bioinformatics-relevant articles were also reviewed to identify additional sources with direct clinical, mechanistic, diagnostic, or computational relevance. Search concepts combined terms for the population, syndrome, diagnostic problem, biological mechanisms, and computational methods. Core search terms included dementia, Alzheimer disease, cognitive impairment, urinary tract infection, UTI, asymptomatic bacteriuria, pyuria, delirium, confusion, functional decline, older adults, nursing home, long-term care, urinary microbiome, metagenomics, PCR, molecular diagnostics, antimicrobial resistance, IL-6, cytokines, neuroinflammation, host response, machine learning, Bayesian inference, knowledge graph, clinical decision support, and diagnostic stewardship.

Sources were included when they informed one or more elements of the dementia-UTI attribution problem: clinical diagnosis of suspected UTI in older adults or dementia populations; distinction between symptomatic UTI, asymptomatic bacteriuria, colonization, pyuria, and contamination; inflammatory or neurobiological mechanisms linking infection to delirium; urinary microbiome, molecular diagnostic, or antimicrobial resistance interpretation; medication, frailty, diabetes, catheter, or comorbidity-related confounding; or computational approaches relevant to probabilistic inference, attribution support, prediction, explainability, and decision thresholds. Sources were excluded when they focused only on uncomplicated UTI in younger adults, addressed non-urinary infections without relevance to the attribution framework, reported analytic test detection without clinical interpretive relevance, lacked peer review, or did not contribute to the conceptual structure of the review.

Evidence was prioritized by clinical proximity and framework relevance. Highest priority was given to guidelines, systematic reviews, and studies involving older adults, long-term care residents, advanced dementia, delirium, asymptomatic bacteriuria, or suspected UTI. Translational evidence from urinary microbiome, molecular diagnostics, precision metagenomics, host-response biomarkers, antimicrobial resistance, medication burden, diabetes, frailty, and catheter-associated urinary disease was used to identify variables that may improve attribution. Computational and knowledge-graph literature was used to inform the architecture of future inference systems, not to imply that a validated dementia-specific UTI diagnostic model already

exists. No formal meta-analysis, risk-of-bias scoring, or PRISMA flow diagram was performed because the purpose of the review was conceptual integration rather than quantitative effect estimation.

Selected studies informed the framework as follows: geriatric UTI, asymptomatic bacteriuria, and delirium studies informed the signal-to-noise and diagnostic-stewardship logic; inflammatory and neurobiological studies informed the neuroinflammatory-burden construct; microbiome, metagenomic, molecular diagnostic, and antimicrobial-resistance studies informed the host-microbial and omics components; medication, frailty, diabetes, catheter, and comorbidity studies informed the competing-cause and confounding domains; sepsis and antimicrobial-stewardship literature informed treatment-threshold logic; and machine-learning, Bayesian, and knowledge-graph studies informed the future computational-inference architecture.

For purposes of synthesis, evidence was classified into two tiers. Direct or clinically proximal evidence comprised studies of dementia, advanced dementia, older adults, long-term care residents, delirium, suspected UTI, and asymptomatic bacteriuria; these sources were used to define the immediate diagnostic and antimicrobial-stewardship problem. Indirect or translational evidence comprised studies of precision metagenomics, fungal UTI, diabetes and SGLT2 inhibitor exposure, renal transplant complicated UTI, diaper-based urine collection, resistance-marker assays, machine learning, and knowledge graphs; these sources were used only to identify candidate mechanisms, variables, technologies, or implementation strategies. Indirect evidence was not treated as validation of the proposed framework, diagnostic accuracy, clinical utility, or patient benefit in dementia.

Table 1. Evidentiary role of source domains in the conceptual framework.

Evidence class	Included evidence domains	Role in this review	Inferences not supported
Direct or clinically proximal	Dementia, advanced dementia, older adults, long-term care, delirium, suspected UTI, and asymptomatic bacteriuria	Defines the immediate diagnostic problem, competing causes, treatment uncertainty, and stewardship context	Does not independently validate a diagnostic model or establish individual-level causality
Indirect or translational	Precision metagenomics, fungal UTI, diabetes and SGLT2 inhibitors, renal transplant UTI, diaper-based collection, resistance assays, machine learning, and knowledge graphs	Identifies candidate mechanisms, variables, technologies, and implementation strategies	Does not establish dementia-specific diagnostic accuracy, clinical utility, treatment benefit, or improved outcomes

The organizing premise is diagnostic stewardship. Diagnostic stewardship emphasizes not only ordering the right test for the right patient, but also interpreting the result in a way that leads to the right clinical action. This premise is especially important in dementia because the same urine result can carry different meanings depending on clinical stability, symptom attribution, host vulnerability, medication burden, and competing diagnoses. A positive culture in a stable patient with chronic bacteriuria and no urinary syndrome may represent colonization. The same culture pattern in a patient with fever, flank pain, leukocytosis, and physiologic decline may support treatment. This review therefore treats the laboratory result as part of the diagnostic intervention rather than as a passive output after testing.

2.2. Conceptual Framework, Scope, and Intended Use

The framework developed here is a conceptual scaffold for probabilistic clinical attribution under uncertainty, not a validated diagnostic model and not empirical proof of causality. It uses signal-to-noise logic, Bayesian updating, neuroinflammatory burden, and decision-threshold concepts to make explicit the inferential problem created when urine positivity, dementia, delirium, and competing causes of decline overlap. The formulas organize the attribution problem into testable components; they are not calibrated clinical calculators or performance-validated prediction equations.

The intended use of the framework(Figure 1) is therefore scientific and translational, consistent with the goals of translational bioinformatics, which seeks to convert complex biomedical and clinical data into actionable knowledge [15]. A useful dementia-UTI attribution tool would need to distinguish organism detection from disease attribution, separate stable low-certainty episodes from high-risk invasive phenotypes, integrate host-response and microbial data, account for medication and metabolic confounding, and support treatment, observation, escalation, or de-escalation within real care workflows.

Claims in this manuscript are calibrated to the stated evidence hierarchy. Direct or clinically proximal evidence supports statements about the immediate diagnostic and stewardship problem in dementia and geriatric care. Indirect or translational evidence supports only hypotheses about candidate mechanisms, variables, technologies, and implementation strategies. No indirect source is interpreted as demonstrating that the proposed framework distinguishes symptomatic UTI from asymptomatic bacteriuria, predicts delirium, reduces antibiotic exposure, or improves clinical outcomes in dementia.

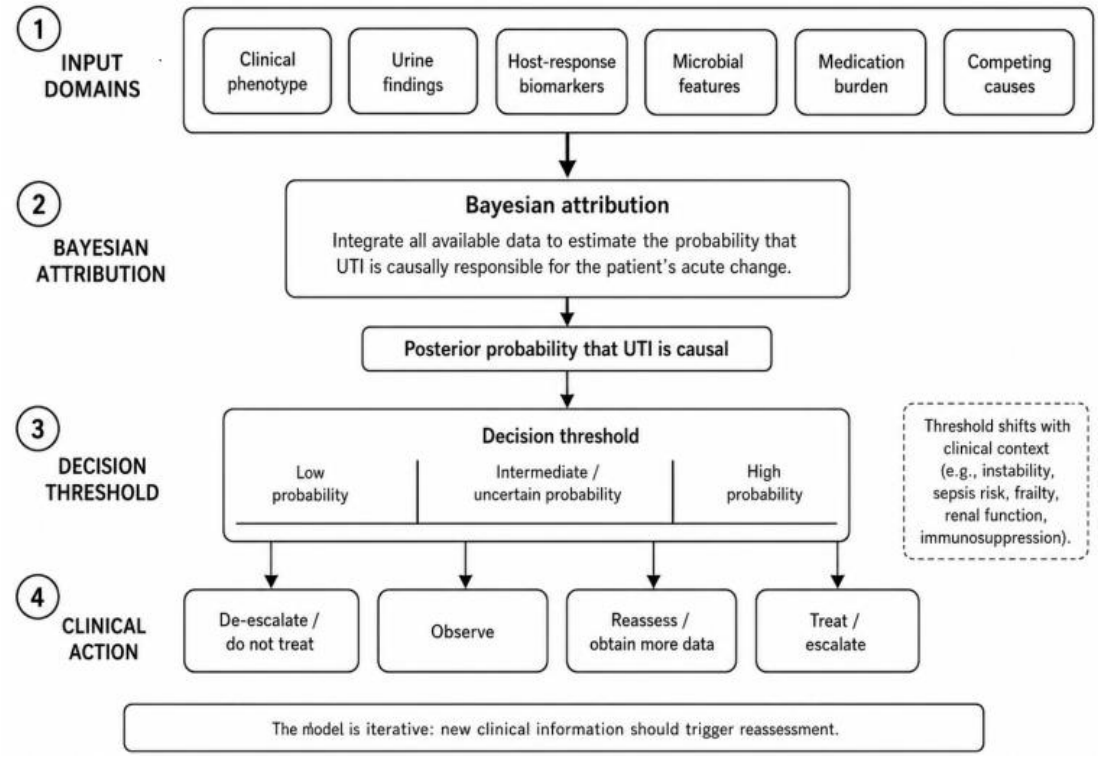

Figure 1. Conceptual Model for Clinical Attribution Under Uncertainty in Suspected UTI and Dementia. Clinical phenotype, urine findings, host-response biomarkers, microbial features, medication burden, and competing causes are integrated through Bayesian updating to estimate the probability of clinically

attributable UTI. Decision thresholds map that estimate and the patient's clinical context to de-escalation, observation, reassessment, treatment, or escalation. The model is conceptual and has not been empirically calibrated or clinically validated.

3. RESULTS

3.1. UTI and Dementia as a High-Noise Biological System

In cognitively intact adults, lower UTI is often anchored by localized symptoms such as dysuria, urgency, suprapubic discomfort, or flank pain. In dementia, those anchors are less reliable. Symptom reporting may be impaired, baseline urinary dysfunction is common, and changes in behaviour or function may substitute for classic urinary complaints.

The diagnostic signal is further weakened because urinary function in dementia is shaped by multiple overlapping conditions. Dementia subtype, immobility, constipation, catheter exposure, medication burden, and metabolic disease can each alter voiding patterns or increase urinary stasis. Lewy body dementia is especially relevant because autonomic dysfunction may produce urinary incontinence and constipation, which can mimic infection-related decline or increase UTI risk through retention and stasis [16].

Diabetes provides an indirect, translational example of how metabolic and pharmacologic factors may modify the attribution problem. Evidence from diabetes and SGLT2 inhibitor studies suggests that glycemic control, glycosuria, medication class, and immune function can alter urinary ecology and infection susceptibility. Diabetes may also impair neutrophil function, toll-like receptor signaling, and phagocytic clearance [9]. These findings support including metabolic status and medication exposure as candidate modifiers in future dementia-specific studies, but they do not establish diagnostic performance or causal attribution in dementia.

These factors create a high-noise diagnostic environment. The relevant signal is not urine positivity itself, but convergent evidence that a urinary process is clinically attributable to the patient's acute decline. Such evidence may include a plausible urinary syndrome, compatible inflammatory findings, actionable microbiology, physiologic instability, or a clinical trajectory that supports infection rather than colonization. And the noise is substantial. Bacteriuria may reflect colonization or asymptomatic bacteriuria [3]. Pyuria may be chronic rather than diagnostic [17]. Specimens may be contaminated or difficult to obtain cleanly. Catheter-associated bacteriuria may represent device colonization rather than invasive disease [18]. Baseline dementia behaviors, noninfectiousdelirium, dehydration, medication effects, urinary retention, and diagnostic anchoring can all make urine results appear more diagnostically explanatory than the evidence supports. In signal-detection terms, the problem can be represented as:

$$SNR_{UTI} = \frac{S_{infection}}{N_{colonization} + N_{ASB} + N_{confounding} + N_{sampling} + N_{anchoring}}$$

where SNR_{UTI} is the diagnostic signal-to-noise ratio, $S_{infection}$ represents evidence of true symptomatic infection, $N_{colonization}$ reflects microbial presence without disease, N_{ASB} reflects asymptomatic bacteriuria, $N_{confounding}$ reflects competing causes of delirium or decline, $N_{sampling}$ reflects contamination or low-quality specimens, and $N_{anchoring}$ reflects cognitive bias toward the urine result.

This equation is conceptual rather than clinically calibrated. The diagnostic task is to estimate clinical attribution.

In this framework, diagnostic accuracy improves by making the signal stronger and the noise more interpretable. The signal strengthens when evidence converges around attributable infection through a plausible urinary syndrome, compatible host response, actionable microbiology, physiologic instability, or a trajectory consistent with infection. The noise decreases when clinicians and computational systems account for colonization, asymptomatic bacteriuria, sampling quality, competing diagnoses, medication effects, and baseline dementia-related behaviors. Urine positivity is one data point within that broader signal environment.

3.2. Neuroinflammation as the Mechanistic Bridge

Systemic inflammation provides the strongest mechanistic bridge between UTI and acute cognitive decline. Aging is associated with immunosenescence and chronic low-grade inflammatory activation, often described as inflammaging [19,20]. In dementia, this inflammatory background may interact with primed microglia, impaired blood-brain barrier regulation, and reduced neuronal reserve. As a result, a peripheral infection can produce a neurocognitive effect that is disproportionate to the apparent severity of the urinary syndrome.Interleukin-6 is especially relevant to this pathway. In a murine model of UTI, IL-6 was implicated in delirium-like phenotypes, providing mechanistic evidence consistent with an inflammatory link between urinary infection and acute neurobehavioral change [21]. Human biomarker studies also suggest that urinary IL-6 may help distinguish symptomatic UTI from asymptomatic bacteriuria in older adults, although its performance is not sufficient to replace clinical judgment [22,23].

This inflammatory logic must still be interpreted cautiously. Frailty, immunosenescence, and immunosuppressive therapies may blunt cytokine signaling or produce atypical inflammatory patterns. For example, calcineurin inhibitors, mycophenolate mofetil, and corticosteroids can suppress T-cell signaling, lymphocyte proliferation, NF-κB activation, and cytokine release, including IL-6 and TNF-α [9]. Thus, a weak inflammatory signal does not necessarily exclude clinically meaningful infection in patients with impaired host response. The bioinformatics task is therefore not simply to measure inflammation, but to interpret host-response signals within the patient's immune reserve, frailty state, and clinical trajectory. A computational representation of neuroinflammatory burden can be specified as:

$$NIB(t) = \sum_{k=1}^{m} w_k \, z\big(C_k(t)\big) + \lambda BBB(t) + \mu M_g(t) + \theta F(t)$$

where $NIB(t)$represents neuroinflammatory burden at time t. $C_k(t)$represents the concentration of inflammatory marker k, such as IL-6, TNF-α, IL-1β, CRP, or heparin-binding protein. The term $z\big(C_k(t)\big)$means that each marker is standardized before being combined, since different biomarkers are measured on different biological scales. The coefficient $w_k$represents the relative weight assigned to each marker. $BBB(t)$represents blood-brain barrier vulnerability, $M_g(t)$represents microglial activation state, and $F(t)$represents frailty or reduced physiologic reserve. The parameters λ, μ, and θ weight the contribution of those vulnerability domains.

The formula emphasizes that delirium risk is unlikely to be determined by organism detection alone. A patient with dementia and chronic bacteriuria may remain cognitively stable until systemic inflammation exceeds the patient's neurocognitive reserve. Conversely, microbial detection without a corresponding host-response signal may represent colonization, asymptomatic bacteriuria, or noncausal microbial presence not clinically attributable to the acute syndrome. The diagnostic target is therefore not simply "microbe detected," but a urinary microbial finding accompanied by a clinically meaningful host-response pattern.

3.3. Bayesian Updating for Causal Attribution

If UTI and dementia form a high-noise biological system, diagnosis cannot depend on a single positive urine result. The interpretive problem is probabilistic. And each new piece of evidence should update the estimated likelihood that the presentation is clinically attributable to UTI. Bayesian reasoning is useful because it separates microbial detection from clinical attribution without claiming empirical proof of causality.

Traditional UTI diagnosis often functions as a rule-based sequence—urine positive, antibiotics started. In dementia, this logic is insufficient because the prior probability of bacteriuria is already high. A positive urine result may have limited attributional value unless it is supported by clinical syndrome, host-response evidence, physiologic instability, or a trajectory consistent with infection. Bayesian reasoning provides a more appropriate structure:

$$P(UTI \mid D) = \frac{P(D \mid UTI)P(UTI)}{P(D \mid UTI)P(UTI) + P(D \mid \neg UTI)P(\neg UTI)}$$

where D represents the observed data, including symptoms, urinalysis, culture or molecular detection, biomarkers, vital signs, medications, and cognitive trajectory. $P(UTI \mid D)$represents the posterior probability that UTI is clinically present after the available evidence is considered. This probability increases when the data are more consistent with true infection than with colonization, asymptomatic bacteriuria, medication toxicity, dehydration, urinary retention, constipation, or baseline dementia-related change.A future, empirically trained bioinformatics model could estimate patient-specific attribution rather than binary urine positivity:

$$P(U_i = 1 \mid X_i)$$
$$= \sigma\left(\beta_0 + \beta_1 X_{\text{clinical}} + \beta_2 X_{\text{UA}} + \beta_3 X_{\text{microbial}} + \beta_4 X_{\text{host}} + \beta_5 X_{\text{microbiome}} + \beta_6 X_{\text{medication}} + \beta_7 X_{\text{trajectory}}\right)$$

where $U_i = 1$ denotes clinically attributable UTI for patient i, $X_i$represents the patient-specific data vector, and σ is the logistic function. The model domains include clinical phenotype, urinalysis, culture or molecular detection, host-response biomarkers, microbiome features, medication exposures, and longitudinal trajectory.This formulation extends our central thesis. The relevant diagnostic question is whether the total pattern of evidence supports clinically attributable UTI. Bayesian updating provides a transparent way to revise that probability as evidence accumulates, while bioinformatics provides an architecture for integrating heterogeneous data into an interpretable patient-specific estimate.

3.4. Multi-Omics and the Urinary Microbiome

The urinary tract is no longer understood as biologically sterile. Urinary microbiome studies show that microbial communities vary with aging, residence setting, urinary symptoms, and disease state. In older adults, especially those living in nursing homes, urinary microbial profiles may shift over time and may include organisms with greater pathogenic potential [24,25]. This matters for dementia-associated UTI because the diagnostic question is not simply whether bacteria are present. The more important question is whether the urinary microbial state is stable colonization, asymptomatic bacteriuria, evolving infection, or part of a broader inflammatory phenotype.

This shift has bioinformatics implications. Standard UTI testing is optimized to identify dominant aerobic uropathogens. It is less suited to characterize polymicrobial communities, fastidious organisms, microbial interactions, resistance gene reservoirs, or functional virulence pathways. This limitation is especially relevant in recurrent, complicated, or persistent UTI, where prior antibiotic exposure and difficult-to-culture organisms may leave clinically meaningful infection unresolved [26,27]. In dementia, however, broader detection alone does not solve the attribution

problem. A richer microbial signal must still be interpreted against clinical phenotype, host response, and competing causes of decline.

Precision metagenomics is included here as translational rather than dementia-specific evidence. In selected clinically suspected UTI samples, it may broaden pathogen detection and characterize polymicrobial or resistance features beyond standard culture or targeted PCR [28]. This evidence supports evaluating metagenomic variables in future dementia cohorts, but it does not establish that metagenomics distinguishes symptomatic UTI from asymptomatic bacteriuria, attributes delirium to UTI, or improves clinical outcomes in dementia.

A multi-omics representation of UTI-related cognitive risk can be expressed as:

$$R_{\text{delirium}} = f(G, T, P, M_b, Met, EHR)$$

where R_{delirium}represents risk of delirium or acute cognitive deterioration. G represents host genomics. T represents transcriptomics. Prepresents proteomics. $M_b$represents microbiome and metagenomic features. Met represents metabolomics. EHR represents structured and unstructured clinical data. In a dementia cohort, these domains could include APOE genotype, inflammatory polymorphisms, cytokine expression, urinary IL-6, CRP, heparin-binding protein, microbial diversity, uropathogen abundance, antimicrobial resistance markers, medication burden, and longitudinal cognitive or functional trajectory.

The challenge is integration. Multi-omics data are high-dimensional, sparse, batch-sensitive, and often collected at different times. A useful model must therefore compress complex biological information without erasing clinical meaning. One approach is to summarize each data layer as a latent representation:

$$Z_j = \phi_j(X_j)$$

where X_j represents a specific data layer, such as metagenomics, proteomics, or EHR-derived clinical features. $\phi_j$represents an embedding function that maps that high-dimensional data layer into a lower-dimensional representation, Z_j, while preserving the features most relevant to attribution.

These latent representations could then be integrated into a final prediction model:

$$\hat{Y} = \Psi(Z_{\text{clinical}}, Z_{\text{urine}}, Z_{\text{host}}, Z_{\text{microbiome}}, Z_{\text{medication}}, Z_{\text{trajectory}})$$

where $\hat{Y}$represents the predicted probability that UTI contributes to delirium or infection-related clinical deterioration. This conceptual formulation extends the central thesis: the goal is not broader microbial detection for its own sake, but computational integration of microbial, host, clinical, and temporal signals into an interpretable estimate of clinical attribution under uncertainty.

4. DISCUSSION

4.1. Molecular Diagnostics: More Detection Is Not Always More Meaning

The preceding sections establish a central implication for diagnostic strategy: in dementia-associated UTI, the value of a test depends less on how much it detects and more on whether its findings improve attribution. Molecular diagnostics offer speed, sensitivity, and broader organism detection, but those advantages can become liabilities when applied to populations with high baseline rates of bacteriuria, colonization, and nonspecific clinical change.

Fungal and resistance-marker evidence is indirect with respect to dementia-specific UTI attribution. Studies involving diabetes, catheter-associated disease, recurrent infection, or immunocompromised populations may identify fungal species, biofilm-associated traits, bacterial resistance genes, and antifungal resistance markers that could inform future attribution models

[8,26,27]. These findings justify the investigation of candidate microbial and resistance variables, but they do not establish that such testing improves causal attribution, antimicrobial decisions, or patient outcomes in dementia.

A positive molecular result may reflect colonization, residual microbial DNA, or a noncontributory polymicrobial urinary state.This concern is reflected in recent commentaries and consensus statements cautioning against routine urine PCR testing in post-acute and long-term care settings when clinical criteria are poorly defined or absent [29,30].

This does not argue against molecular testing. It argues for decision-grade molecular testing. A molecular result has decision-grade value only when it changes interpretation or management beyond what clinical assessment, urinalysis, and culture already provide. Examples include recurrent or refractory symptoms with negative culture, suspected fastidious organisms, prior multidrug-resistant pathogens, complicated UTI with high penalty for delay, or discordance between clinical severity and conventional microbiology. In these contexts, molecular testing can support escalation, de-escalation, antimicrobial selection, source evaluation, or stewardship review.

This decision-grade logic also applies to fungal and resistance-marker detection. In high-risk urinary environments, particularly diabetes, catheter-associated disease, recurrent infection, or immunocompromise, molecular testing may need to identify fungal species, biofilm-associated traits, bacterial resistance genes, and antifungal resistance markers. These findings are clinically relevant only when they alter the interpretation of candiduria, the likelihood of persistent infection, antimicrobial selection, catheter management, or escalation of care [27]. The key bioinformatics principle is therefore straightforward: clinical validity is not equivalent to analytic detection.

Decision-grade value can be expressed as:

$$DGV = I\left(A_{\text{post}} \neq A_{\text{pre}}\right) \times \Delta NB$$

Expanded explicitly, this means:

$$DGV = \begin{cases} \Delta NB, & \text{if } A_{\text{post}} \neq A_{\text{pre}} \\ 0, & \text{if } A_{\text{post}} = A_{\text{pre}} \end{cases}$$

Where DGV represents decision-grade value. A_{pre} is the intended clinical action before molecular testing, and A_{post} is the clinical action after molecular results are available. The term $I(A_{\text{post}} \neq A_{\text{pre}})$ is an indicator function. It equals 1 when the test changes management and 0 when it does not. ΔNB represents the change in net clinical benefit produced by the test-informed decision.

In practical terms, a molecular test has high decision-grade value when it changes a meaningful clinical action and improves net benefit. This may include stopping antibiotics, narrowing therapy, escalating treatment, identifying resistance, redirecting the work-up, changing catheter management, or preventing unnecessary admission. If a molecular panel detects additional organisms but does not alter treatment, de-escalation, source evaluation, admission decisions, or stewardship action, its decision-grade value is low:

$$A_{\text{post}} = A_{\text{pre}} \Rightarrow DGV = 0$$

The purpose is to convert microbial information into better probabilistic clinical interpretation and better clinical action.

4.2. Antimicrobial Decision Thresholds

The UTI-dementia paradox is not simply a problem of overtreatment. It is a dual-risk problem. In stable, low-certainty presentations, antibiotics may expose patients to harm without treating the true cause of decline. Yet when invasive infection is evolving, delayed therapy may carry substantial clinical consequences. The diagnostic challenge is therefore inseparable from the treatment threshold: clinicians must decide when the probability of attributable UTI is high enough to justify antimicrobial therapy.

This threshold should not be fixed. It should shift according to clinical severity, host vulnerability, physiologic stability, and the consequences of delay. Sepsis literature supports this distinction, showing that delayed antibiotics are associated with worse outcomes in high-severity infection phenotypes [31]. Similarly, Surviving Sepsis Campaign guidance emphasizes rapid antimicrobial therapy when sepsis or septic shock is likely, while also supporting time-sensitive assessment when infection probability is uncertain [31].

A decision-theoretic rule can be expressed as:

$$\text{Treat if } P(A_{UTI} \mid D) \times H_{\text{missed}} > (1 - P(A_{UTI} \mid D)) \times H_{\text{ABX}}$$

Where $P(A_{UTI} \mid D)$presents the posterior probability that the patient's presentation is attributable to UTI after considering the available data D. H_{missed} represents the harm of missed or delayed treatment when infection is truly present. H_{ABX} represents the harm of unnecessary antibiotics when the urinary finding is not clinically causal.

The antibiotic harm term includes adverse drug events, Clostridioides difficile infection, resistance selection, microbiome disruption, medication-associated delirium, and treatment cascades. The missed-infection harm term includes progression to pyelonephritis, bacteremia, sepsis, hospitalization, organ injury, or death. In immunocompromised or structurally complicated urinary phenotypes, H_{missed} may be especially high. Evidence from renal transplant complicated UTI is used here as an indirect high-risk comparator illustrating the competing harms of delayed treatment and unnecessary broad-spectrum therapy [10]. It does not define or validate antimicrobial treatment thresholds for patients with dementia. The example therefore supports the general decision-theoretic principle, not a dementia-specific clinical threshold.

The same decision rule can be rearranged into a treatment threshold:

$$P(A_{UTI} \mid D) > \frac{H_{\text{ABX}}}{H_{\text{missed}} + H_{\text{ABX}}}$$

This equation clarifies why the same urine result may justify different actions in different patients. In a stable patient with chronic bacteriuria, no localizing urinary features, and a plausible noninfectious explanation for delirium, H_{ABX} may dominate. The treatment threshold should therefore remain high. In contrast, when hypotension, persistent fever, rising lactate, leukocytosis, flank pain, or other signs of invasive infection are present, H_{missed} dominates. The treatment threshold falls, and antibiotics should begin promptly while cultures and source evaluation proceed.

This section extends the central thesis from diagnosis to action. If suspected UTI in dementia is a probabilistic attribution problem, then antimicrobial treatment must also be governed by probabilistic thresholds. Bioinformatics can support this process by estimating attribution probability, identifying high-risk phenotypes, and linking diagnostic evidence to patient-specific decisions about treatment, observation, escalation, or de-escalation.

4.3. Medication Burden and False UTI Phenotypes

Medication burden is a critical source of diagnostic noise in dementia-associated UTI. Many drugs commonly used in older adults can generate both neurocognitive change and urinary dysfunction, thereby producing a clinical phenotype that resembles infection without being infectious. Anticholinergic agents, sedatives, opioids, antipsychotics, and cumulative polypharmacy can contribute to delirium, urinary retention, constipation, falls, reduced mobility, and functional decline. These effects are especially consequential in dementia, where symptom reporting is impaired and clinicians may rely heavily on nonspecific behavioral or functional change.

The problem is not simply that medications confound diagnosis. Rather, medications can create a false UTI phenotype. Anticholinergic burden is strongly relevant because it can impair cognition while also worsening urinary retention or incontinence. This makes it biologically plausible for a medication effect to trigger urine testing and then be misattributed to bacteriuria. Evidence linking anticholinergic burden to delirium supports medication exposure as a necessary variable in attribution models [33]. Prescribing cascades further intensify this risk. In dementia care, cholinesterase inhibitors may contribute to urinary symptoms, which may then prompt anticholinergic treatment for incontinence, thereby worsening cognition and increasing the likelihood of further diagnostic misclassification [34].This pathway can be represented as:

$$Medication\ Exposure \rightarrow Urinary\ Dysfunction + Cognitive\ Change \rightarrow Urine\ Testing \rightarrow Antibiotic\ Treatment$$

More explicitly:

$$X_{\text{medication}} \rightarrow \left(Y_{\text{urinary}} + Y_{\text{cognitive}}\right) \rightarrow T_{\text{urine}} \rightarrow A_{\text{antibiotic}}$$

where $X_{medication}$ represents medication exposure or medication burden, $y_{urinary}$ represents urinary symptoms or urinary dys function, y represents delirium or cognitive-functional decline, T_{urine} represents urine testing, and $A_{antibiotic}$ represents antibiotic initiation.
Without computational recognition of this pathway, a decision system may incorrectly treat medication-induced delirium, retention, constipation, or falls as evidence of UTI. A bioinformatics attribution model should therefore encode medication burden as more than a passive covariate. It should include anticholinergic load, recent medication starts or dose changes, sedative exposure, opioid exposure, antipsychotic use, diuretic changes, cholinesterase inhibitor use, and evidence of prescribing cascades. This extends the central thesis of the manuscript: UTI attribution in dementia requires integration of microbial data with host state, clinical trajectory, and competing explanations. Medication burden is one of the most important competing explanations because it can imitate both sides of the UTI phenotype: urinary dysfunction and acute cognitive decline.

4.4. Knowledge Graphs for Clinical Inference Support

The knowledge-graph literature reviewed here is indirect and computational. It is used to identify a possible architecture for explainable future inference, not to claim that a dementia-UTI knowledge graph has been trained, validated, or shown to improve clinical decisions or patient outcomes.The preceding sections treat UTI attribution in dementia as a probabilistic clinical-inference problem. A knowledge graph provides a useful architecture for that problem because it can represent relationships that are difficult to capture in a flat prediction model. Suspected UTI in dementia is not determined by one variable. It emerges from the interaction of dementia subtype, symptom-reporting capacity, urinary function, medication exposure, microbial findings, host-response biomarkers, comorbid disease, and clinical trajectory. A knowledge graph can organize these heterogeneous signals into an interpretable structure.

Biomedical knowledge graphs are especially relevant because they represent entities and relationships rather than isolated variables. In this framework, entities may include diseases, symptoms, medications, pathogens, resistance genes, biomarkers, diagnostic tests, physiologic states, and clinical outcomes. Relationships may encode associations, putative mechanistic links, mimicry, diagnostic support, contraindications, escalation risk, or the need for follow-up. PrimeKG, for example, integrates multimodal biomedical resources to support precision medicine reasoning across diseases, drugs, genes, and biological processes [35]. Broader healthcare knowledge graph literature similarly emphasizes the value of integrating heterogeneous biomedical and clinical data for decision support and inference [36].

For dementia-associated UTI, the central value of a knowledge graph is not simply prediction. Its value is structured explanation. A conventional model may output a risk score, but it may not show why that score is clinically plausible. A knowledge graph can make the reasoning pathway visible. It can show whether the evidence supports infection, colonization, medication toxicity, dehydration, urinary retention, constipation, or another competing explanation for decline.

Formally, a knowledge graph can be represented as:

$$KG = (V, E, R)$$

Where V is the set of biomedical entities, E is the set of edges connecting those entities, and R is the set of relation types that define the meaning of each connection.
In a dementia-UTI graph, V could include dementia subtype, delirium phenotype, urinary symptoms, pyuria threshold, urine culture result, PCR result, metagenomic organism profile, resistance gene, IL-6, CRP, heparin-binding protein, catheter status, anticholinergic burden, hydration state, constipation, diabetes, glycosuria, sepsis physiology, antibiotic exposure, and clinical outcome. The relation set Rcould include “increases risk of,” “mimics,” “supports,” “weakens,” “requires follow-up,” “suggests alternate source,” “contraindicates,” or “increases urgency of treatment.”
Several patient-specific reasoning paths illustrate the value of this architecture:

$$Dementia \rightarrow Impaired\ Symptom\ Reporting \rightarrow Low\ Symptom\ Focality$$

$$Anticholinergic\ Burden \rightarrow Urinary\ Retention \rightarrow Bacteriuria$$

$$Dehydration \rightarrow Delirium \rightarrow Urine\ Testing \rightarrow Incidental\ Bacteriuria$$

$$Fever + Flank\ Pain + Pyuria + Monomicrobial\ Growth + IL6 \uparrow \rightarrow Higher\ UTI\ Attribution$$

These paths clarify why the same urine result can have different meanings in different patients. In one patient, bacteriuria may be explained by urinary retention caused by anticholinergic exposure. In another, the same bacteriuria may become clinically meaningful when paired with fever, flank pain, rising inflammatory markers, and physiologic instability. The knowledge graph therefore supports contextual interpretation rather than reflex classification.

This is important for explainable clinical AI. A conventional prediction model may classify a patient as high risk for UTI-attributable delirium without showing how that conclusion was reached. A knowledge graph-enhanced model should instead expose the reasoning pathway. It should show whether attribution is strengthened by convergent infection evidence, such as fever, pyuria above threshold, monomicrobial uropathogen detection, rising IL-6, or physiologic instability. It should also show whether attribution is weakened by competing explanations, such as chronic bacteriuria, absence of a urinary syndrome, recent sedative escalation, dehydration, constipation, urinary retention, or stable vital signs.

The value of the knowledge graph is therefore not merely that it can support prediction. Its value is that it can make prediction clinically interpretable. In dementia-associated UTI, this interpretability is essential because the same urine result may support treatment in one patient, observation in another, and de-escalation in a third. The model must therefore explain how microbial evidence, host response, medication burden, competing diagnoses, and clinical trajectory interact to strengthen or weaken clinical attribution.

The inferential goal can be represented as:

$$P(A_{UTI} \mid D, KG)$$

Where $P(AUTI \mid D,KG)$ represents the probability that the patient's acute decline is attributable to UTI after integrating observed clinical data D with the relational structure of the knowledge graph KG. This formulation extends the Bayesian argument by adding biomedical context. The model does not only ask which variables are present. It asks how those variables relate to one another in a biologically and clinically plausible relational structure. Knowledge graphs are therefore a prospective implementation strategy requiring dementia-specific evaluation.

4.5. Implementation Blueprint Derived from the Conceptual Framework

The five-layer structure proposed here should be read as an implementation blueprint derived from the conceptual framework, not as a validated diagnostic model or deployable clinical decision-support system. Its purpose is to identify the clinical, laboratory, biological, computational, and decision-support domains that future dementia-specific UTI attribution tools would need to integrate. The architecture would include five layers. First, the clinical phenotype layer should encode acute change from baseline, delirium score, urinary symptoms, hydration, pain, constipation, falls, respiratory symptoms, neurologic signs, catheter status, frailty, dementia subtype, and vital signs. Sample acquisition should also be considered a candidate diagnostic variable. Many patients with moderate to advanced dementia are incontinent, immobile, or unable to provide a clean-catch specimen. Diaper-based urine collection studies [37,38] are included as indirect technical-feasibility evidence. They suggest that sodium polyacrylate-based materials may permit molecular recovery of urinary targets, but they do not establish diagnostic accuracy for symptomatic UTI attribution, clinical utility, or improved outcomes in dementia or long-term care. The method therefore requires prospective validation in dementia-specific workflows.

Second, the conventional laboratory layer should include urinalysis, microscopy, urine culture, blood culture when indicated, complete blood count, metabolic panel, lactate, renal function, and inflammatory markers.Third, the host-response and omics layer should include IL-6, CRP,

heparin-binding protein, transcriptomic signatures, proteomics, metabolomics, urinary microbiome features, metagenomic pathogen detection, and antimicrobial resistance markers. Within this layer, extraction-free PCR for CTX-M Group 1 ESBL genes [39] is presented as indirect proof-of-concept evidence for rapid resistance-marker detection. It illustrates a candidate laboratory capability for future architecture development but does not validate resistance-guided decision support in dementia.Fourth, the computational inference layer should combine Bayesian probability estimation, supervised machine learning, time-series modeling, and knowledge graph reasoning. General infectious-disease machine-learning literature provides translational design guidance regarding bias, calibration, explainability, and workflow fit [40]; it does not establish the performance of a dementia-specific UTI attribution model.Fifth, the decision-support layer should produce actionable outputs: withhold antibiotics and reassess, treat immediately, obtain culture, broaden differential, evaluate alternate source, de-escalate, stop therapy, or escalate for sepsis [41]. This mirrors diagnostic stewardship principles in microbiology, where tests should be selected and interpreted in ways that improve patient outcomes rather than simply generate additional results [42]. Four hypothetical cases illustrating how these outputs could differ across clinical contexts are presented in Table 2.

4.6. Worked Clinical Applications of the Conceptual Framework

To illustrate the intended use of the framework, Table 2 applies its attribution logic to four hypothetical clinical scenarios. The resulting classifications are qualitative rather than numerically calibrated because no dementia-specific prediction model or decision threshold has yet been trained or validated. The cases are illustrative and do not replace clinical judgment, established diagnostic criteria, or local treatment protocols.

Table 2. Hypothetical clinical applications of the conceptual UTI-attribution framework

Clinical scenario	Integrated evidence	Framework classification	Illustrative action
1. Stable confusion with asymptomatic bacteriuria	An 86-year-old long-term-care resident with moderate dementia develops new confusion after two days of poor oral intake. The patient is afebrile and hemodynamically stable, with no observed localizing urinary signs, flank tenderness, leukocytosis, or other evidence of systemic infection. Urinalysis shows pyuria, and culture identifies *Escherichia coli*similar to previous cultures. Clinical examination supports dehydration.	Low probability of clinically attributable UTI. The urine findings are more consistent with asymptomatic bacteriuria or an incidental finding, while dehydration is the stronger competing explanation [3,4,6,7].	Withhold antibiotics, correct dehydration, investigate other causes of confusion, and monitor clinically. Reassess if localizing urinary findings, inflammatory evidence, or physiologic instability emerges.

Clinical scenario	Integrated evidence	Framework classification	Illustrative action
2. Delirium with medication-induced urinary retention	A 79-year-old patient with Lewy body dementia develops delirium shortly after initiation of an anticholinergic medication and an increase in opioid dosage. Examination identifies bladder distention and a high post-void residual. The patient is afebrile and stable, without leukocytosis, although pyuria and bacteriuria are present.	Low-to-intermediate probability of UTI attribution. The temporal medication exposure, urinary retention, and absence of systemic inflammatory evidence provide a more plausible clinical explanation than infection. [16,33,34].	Review and reduce or discontinue contributing medications, relieve urinary retention, address constipation and pain, and reassess cognition and urinary function. Antibiotics should not be initiated solely because bacteriuria is present.
3. Physiologic instability with probable invasive UTI	An 83-year-old patient with advanced dementia develops abrupt delirium accompanied by fever, hypotension, tachycardia, flank tenderness, leukocytosis, elevated lactate, pyuria, and a nitrite-positive urine result.	High to very high probability of clinically attributable and potentially invasive UTI. Physiologic instability substantially lowers the treatment threshold because the potential harm of delayed therapy exceeds the likely harm of empiric treatment [31,32].	Obtain urine and blood cultures, initiate empiric antimicrobial therapy and sepsis management without delay, evaluate for alternative or additional infection sources, and escalate the level of care. Narrow, change, or discontinue therapy as microbiological and clinical data become available.
4. Recurrent UTI with potential decision-grade molecular testing	A 76-year-old patient with mild dementia and recurrent culture-confirmed UTI has persistent urinary symptoms after recent antibiotic exposure. Standard culture is negative or reports mixed growth, the patient has a history of a resistant uropathogen, and the clinical condition remains stable.	Intermediate probability of attributable UTI with unresolved microbial uncertainty. Molecular testing may have decision-grade value only when its result is likely to alter antimicrobial selection, de-escalation, source evaluation, or another meaningful clinical action [26,28–30]. Its utility in dementia remains to be validated.	Obtain a high-quality specimen and selectively consider targeted PCR or metagenomic testing. Use the result only when it can narrow, redirect, stop, or escalate treatment. Broad molecular testing should be avoided when additional organism detection would not change management.

Note: All cases are hypothetical. Attribution categories are qualitative and illustrative, not calibrated diagnostic probabilities. ASB, asymptomatic bacteriuria; UTI, urinary tract infection.

Similar urinary findings may support de-escalation, observation, additional testing, treatment, or escalation depending on clinical stability, host response, medication exposure, competing causes, prior probability, and the consequences of delayed treatment.The framework is therefore iterative: new clinical, laboratory, or temporal information should prompt reassessment of both the clinical attribution estimate and the appropriate action.

5. FUTURE RESEARCH AGENDA

This future research agenda is a secondary output of the conceptual framework and specifies the evidence required before dementia-specific UTI attribution models can be developed, validated, or deployed in clinical care. Accordingly, technologies and computational methods derived from adjacent populations should remain candidate inputs until dementia-specific studies demonstrate incremental diagnostic value, calibration, clinical utility, and patient benefit.

The next phase of research should move from descriptive association toward empirically validated clinical attribution. A validation study would require prospective longitudinal cohorts of patients with mild, moderate, and advanced dementia across emergency department, hospital, long-term care, and outpatient settings. Each suspected UTI episode should be paired with standardized delirium measurement, baseline cognitive and functional status, medication review, vital signs, comorbidity assessment, hydration status, and competing-cause evaluation.

Outcome definitions should be specified before model development. Core outcomes should include symptomatic UTI, asymptomatic bacteriuria, delirium severity and duration, hospitalization, sepsis or missed invasive infection, antibiotic initiation, antibiotic days of therapy, de-escalation, adverse drug events, Clostridioides difficile infection, mortality, and return to cognitive or functional baseline. Urine testing protocols should define specimen type, collection quality, urinalysis thresholds, culture criteria, molecular testing indications, resistance-marker interpretation, and repeat-testing rules.

Biomarker and microbiome collection should be timed to the clinical episode and follow-up trajectory. Candidate measures may include inflammatory markers, host-response biomarkers, microbial community features, pathogen burden, antimicrobial resistance markers, and medication or metabolic modifiers. Model development should then assess discrimination, calibration, decision-curve performance, subgroup performance, missing-data handling, explainability, and clinical usability. Reporting of future attribution models should also follow established prediction-model reporting standards such as TRIPOD to improve transparency, reproducibility, and external validation [43].

External validation is essential. Future studies should also assess risk of bias and model applicability using established prediction-model evaluation frameworks such as PROBAST [44].Models should be tested across independent sites, dementia severities, care settings, specimen-collection methods, and patient subgroups before clinical deployment. Patient-centered validation should determine whether the framework reduces unnecessary antibiotics without increasing missed infection, hospitalization, sepsis, adverse drug events, mortality, or caregiver burden. Only after such validation should dementia-specific UTI attribution tools be considered for clinical decision support.

6. CONCLUSION

This review's primary contribution is an integrative conceptual bioinformatics framework for probabilistic clinical attribution of suspected UTI in dementia under uncertainty. The framework organizes the clinical, microbial, host-response, medication, and trajectory evidence needed to interpret suspected UTI in dementia. It does not demonstrate that UTI causes a given neurocognitive episode. Rather, it organizes the evidence needed to estimate whether urinary findings are clinically attributable, potentially contributory, incidental, or misleading.

A secondary contribution is the proposed five-layer implementation blueprint. This architecture identifies the clinical, laboratory, host-response, omics, computational, and decision-support domains that future dementia-specific UTI attribution systems would need to organize. It is not presented as a validated diagnostic model, clinical calculator, or deployable clinical decision-support system. Rather, it specifies the structure that future empirically trained and clinically validated systems would need to satisfy.

The accompanying research agenda is also secondary to the conceptual framework. Future work should validate dementia-specific attribution models using longitudinal clinical cohorts, calibrated prediction methods, molecular diagnostic stewardship, explainable knowledge graphs, and patient-centered outcomes. The future of UTI diagnosis in dementia should therefore move beyond organism detection toward empirically validated clinical attribution under uncertainty, with the goal of treating the right patients at the right time while reducing both delayed-treatment risk and avoidable antimicrobial harm.

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