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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder affecting the entire digestive tract, sometimes with extra-digestive symptoms. In Algeria, its incidence is rising, especially among young adults, with up to **5.32 cases per 100,000 inhabitants** in some regions (1). Treatment aims to induce and maintain remission, with thiopurines like azathioprine commonly prescribed.

However, metabolic variability can lead to therapeutic failure or adverse effects when metabolite levels are not monitored.

Therapeutic Drug Monitoring (TDM) using UHPLC-MS/MS quantification of 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) may improve personalized therapy, prevent unnecessary biologic escalation, and optimize resource use (2). In resource-constrained healthcare systems, pharmacoeconomic evaluation of TDM implementation is crucial for sustainable management.

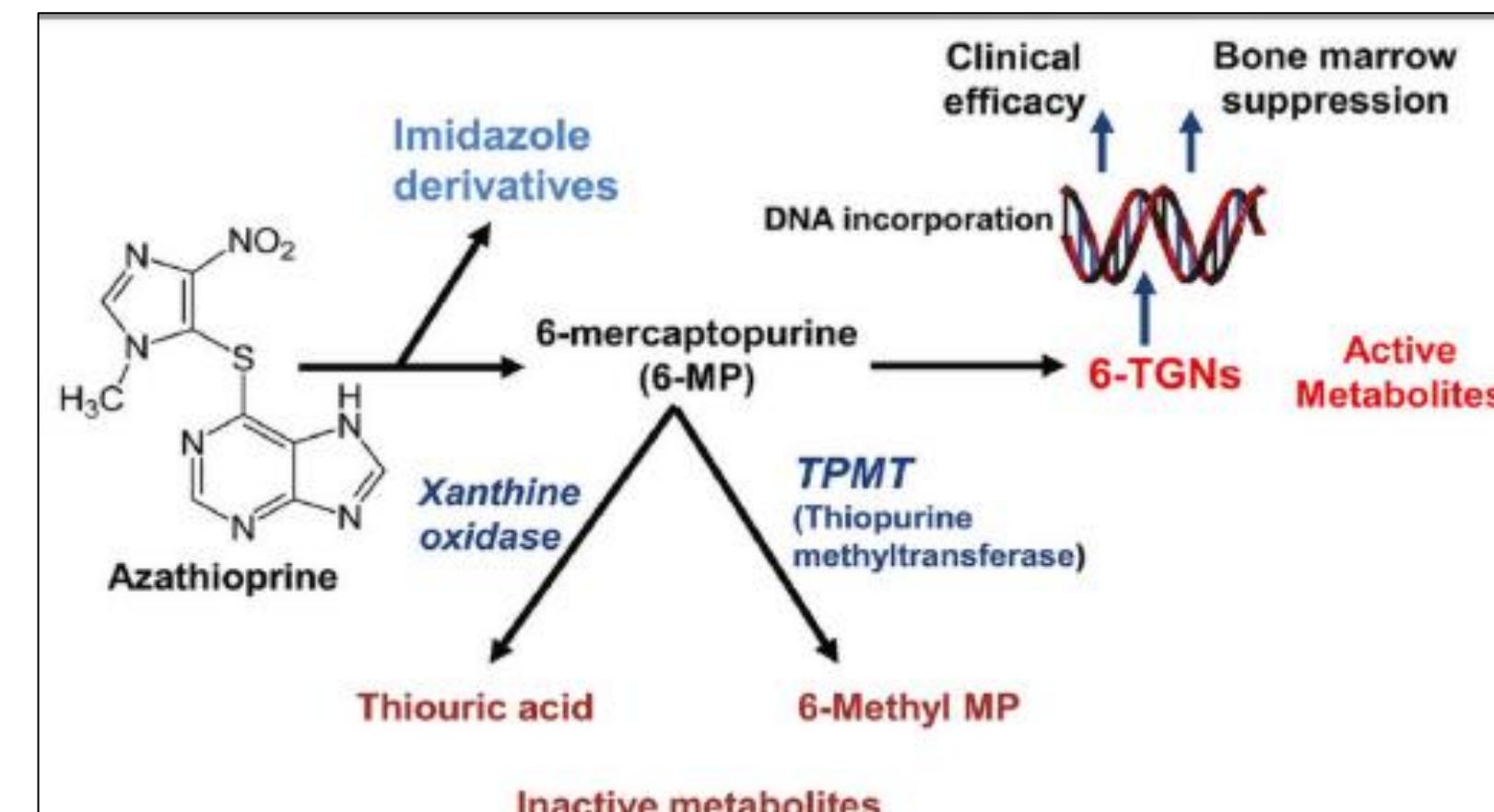


Figure 1. Metabolism pathway of azathioprine

Our study evaluates the cost and economic impact of adding this monitoring to CD management in Algeria.

METHOD

An Excel-based model was developed to estimate the cost of integrating azathioprine metabolite measurement: 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP). Two scenarios were compared over a **5-year horizon** (2025–2029) from **the perspective of the Algerian healthcare payer**:

- **Scenario 1** (Current): standard care without metabolite monitoring
- **Scenario 2** (Optimized): care including TDM of azathioprine metabolites

Target population: Crohn's disease patients treated with azathioprine as first-line therapy, estimated from available epidemiological data and field analysis

A one-way sensitivity analysis was performed by varying unit costs by $\pm 20\%$ for each expense item within the monitoring scenario to assess impact on total cost.

RESULTS AND DISCUSSION

a. Field study and Population eligible for metabolite monitoring

A retrospective analysis was conducted on Crohn's disease patients treated **between 2020 and 2024** at the University hospital center Mohamed Lamine Debaghine and the Public Hospital Establishment Bachir Mentouri Kouba. Among **218 recorded patients**, 55 with complete treatment and demographic data were included in the analysis. Of these, 18.2% switched to adalimumab monotherapy, 10.9% received combination therapy (Azathioprine+Adalimumab), and 70.9% continued azathioprine alone.

Table 1. Eligible population for metabolite monitoring.

Population	2025	2026	2027	2028	2029	Reference
Total Algerian population (100%)	48 120 480	48 851 911	49 594 460	50 348 296	51 113 590	(2)
Population growth rate (1.52%)	1,52%	1,52%	1,52%	1,52%	1,52%	(2)
Incidence of Crohn's disease in Algeria (0.00532%)	2560	2599	2638	2679	2719	(3)
Patients on azathioprine (41.8%)	1070	1086	1103	1120	1137	(4)
Patients on azathioprine as first-line at diagnosis (26.9%)	288	292	297	301	306	(4)

In Our study, treatment, laboratory monitoring, and pre-therapeutic assessments generated variable costs per patient, depending on the therapeutic strategy chosen. The estimated costs were as follow :

- Azathioprine (6 months, 150 mg/day): **923 USD**;
- Pre-anti-TNF α work-up: **342 USD**;
- Adalimumab: 891 USD (monotherapy), **967 USD** (with azathioprine);
- Azathioprine continuation: **255–312 USD** (depending on dose);
- Azathioprine+Allopurinol: **223 USD**;
- Corticosteroids (12-week taper): **348 USD**;
- Mesalazine (6 months): **617 USD**.

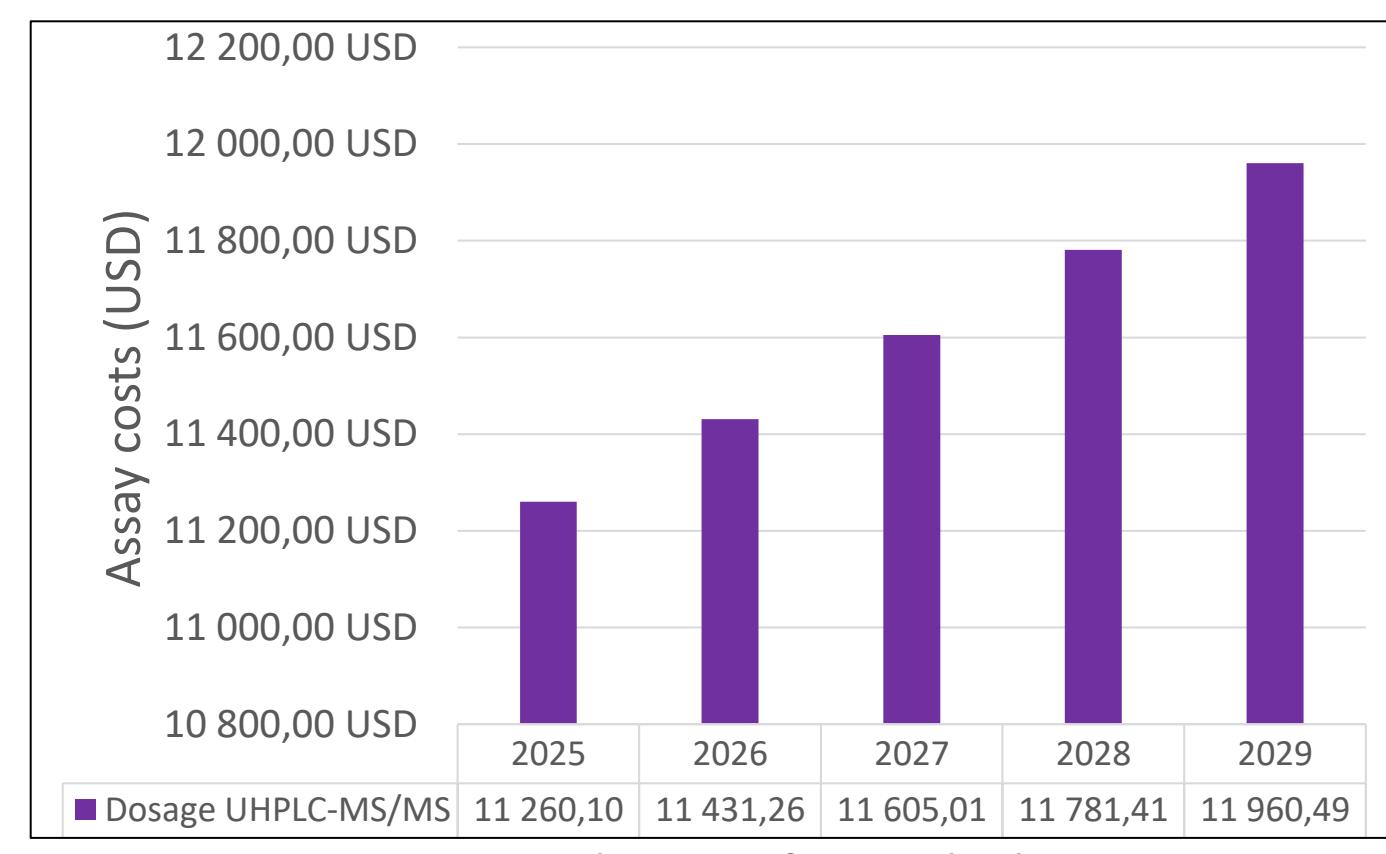
Overall, per-patient costs ranged from **220 to 970 USD**, underscoring the budgetary impact of treatment selection.

b. Estimation of the cost of metabolite monitoring

Category	Item / Description	Quantity	Total Cost (USD)
Implementation (UHPLC-MS/MS)	Triple-quadrupole MS with UPLC system	1	67,725.60
	Analytical columns (C18, 1.8 μ m, 2.1 \times 100mm)	10	10,640.70
	Pre-columns (pack of 3)	20	15,600.00
	ICH M10 validation	1	672.30
Subtotal (USD)		94,668.60	
Calibration & QC	Monthly cost	–	552.10
	Annual cost	–	6,625.50
	Five-year cost	–	33,127.80
Assay per patient		39.13 USD	

c. Monitoring costs

The cost per patient for the quantification of 6-TGN and 6-MMP metabolites by UHPLC-MS/MS was estimated at 39.13 USD. Total annual costs were projected according to the number of patients eligible for the assay over the study time horizon and are presented in **Figure 2**.



d. Incremental Budget over five years

The incremental budget (Future budget - Current budget) is shown in **Figure 4**. The incremental budget increases each year.

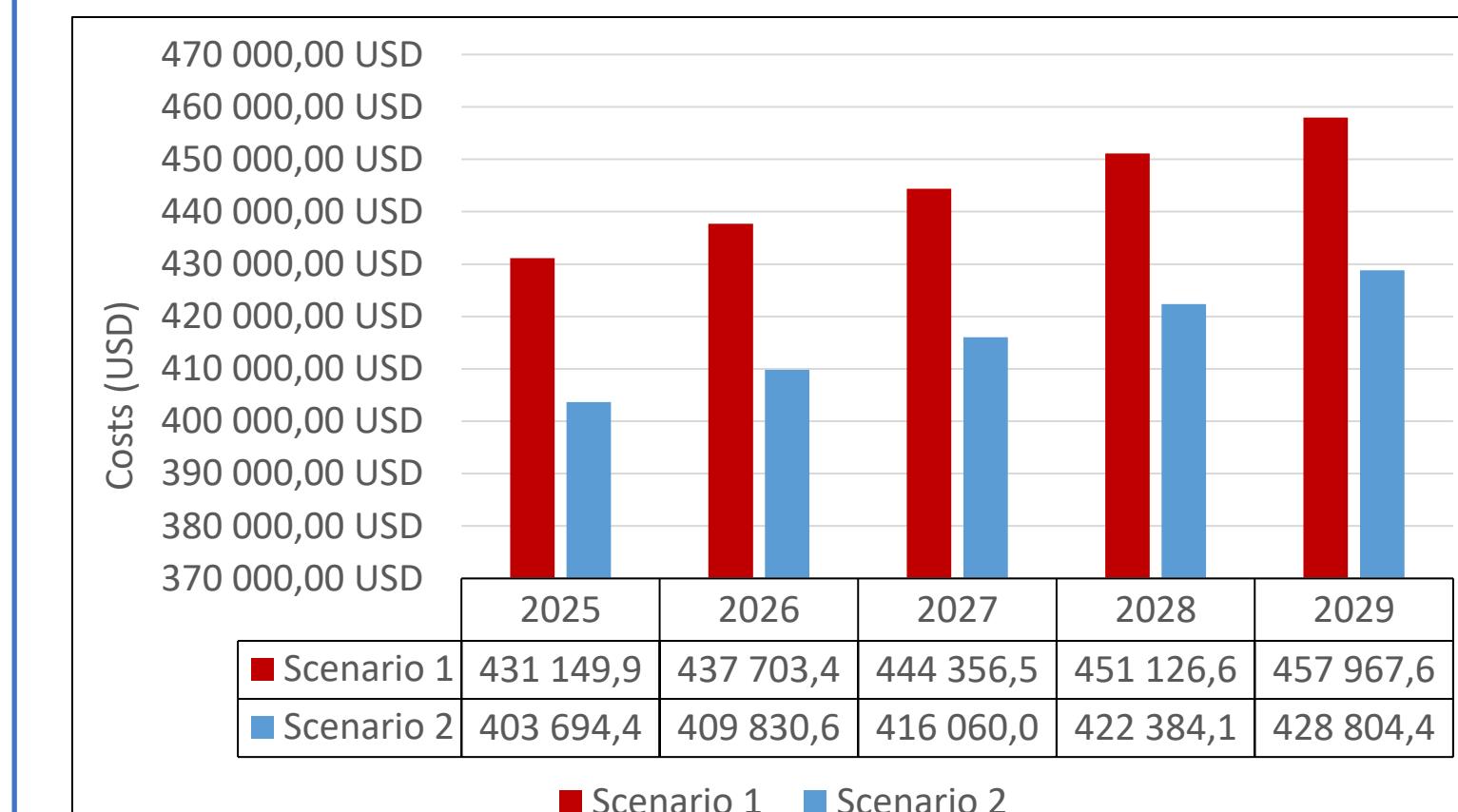


Figure 3. Budget Impact Model scenario over 5 years.

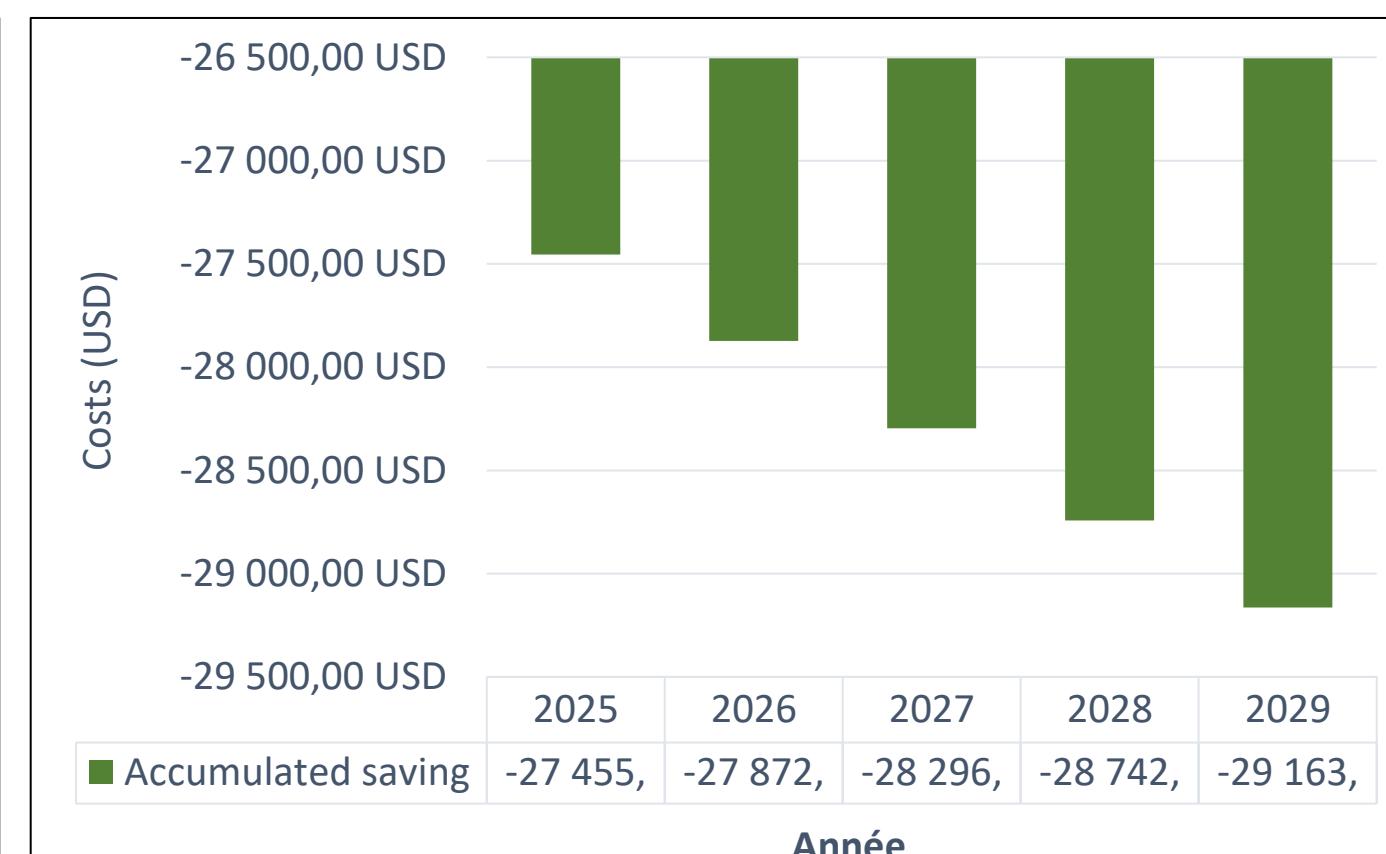


Figure 4. Cumulative savings over 5 years.

e. Sensitivity analysis

As shown in **Figure 5**, the most sensitive budget items were adalimumab monotherapy ($\pm 47,000$ USD) and an increase on azathioprine dosage to 175 mg ($\pm 41,800$ USD). It's important to note that implementing TDM on a national scale would require investments in equipment, training, and personnel across the country. Nevertheless, potential long-term savings associated with adverse event (AE) management and improved clinical outcomes, as suggested by other studies, could offset these initial expenditures.

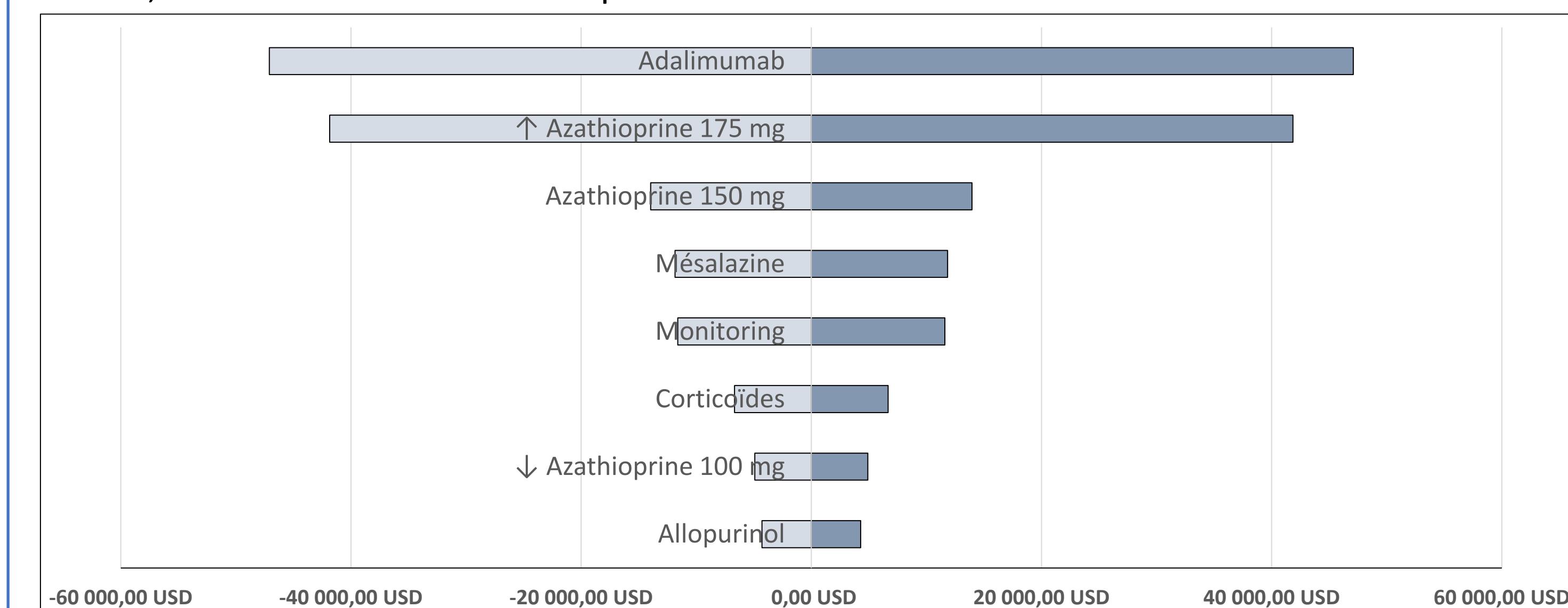


Figure 5. Tornado diagram – Budget impact sensitivity analysis ($\pm 20\%$) of major cost drivers in the scenario with metabolite monitoring (over 5 years)

Over a 5-year horizon, metabolite testing could save more than 138,000 USD compared with standard care. The total cost of the testing strategy was estimated at 2.08 million USD versus 2.22 million USD without TDM, mainly due to reduced reliance on costly biologics. International data support these findings. **In Singapore**, TDM enabled steroid-free remission in 87.8% of IBD patients and avoided treatment escalation or surgery in 90.7%, with per-test costs (100 USD) nearly double those estimated in our study (5). **Dubinsky et al.** reported that TDM-based strategies reduced both the time to clinical response (19 vs 22.4 weeks) and total annual costs (6). **Another pharmacoeconomic analysis** found that metabolite testing alone reduced mean patient costs from 1,146 USD to 225 USD, while improving QALYs. The OPTIC RCT in ulcerative colitis demonstrated substantial societal savings: 1,937 € per additional patient in remission and 15,621 € per QALY gained with thiopurine TDM. (7)

Finally, sensitivity analysis highlighted that high-impact interventions such as adalimumab or high-dose azathioprine drive most budget variability. By contrast, metabolite testing showed only moderate and manageable variation ($\pm 11,500$ USD), reinforcing its stability and economic sustainability, particularly in resource-limited settings such as Algeria.

CONCLUSION

TDM of azathioprine metabolites by UHPLC-MS/MS in CD represents a clinically relevant and cost-effective strategy. Although it requires an initial investment, it reduces therapeutic failures, limits the use of costly biologics, and generates projected savings exceeding 138,000 USD over five years. These findings position TDM as a promising approach to improve care quality and optimize healthcare resource allocation in Algeria.

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REFERENCES

